British Journal of Anaesthesia

Editor of General Issues: A. A. Spence

EDITORIAL BOARD

Editor of General Issues

A. A. SPENCE, *Reader, University Department of Anaesthesia, Western Infirmary, Glasgow*

Editor of Postgraduate Educational Issues

J. NORMAN, *Professor of Anaesthetics, The General Hospital, Tremona Road, Southampton SO9 4XY*

C. M. CONWAY, *Professor of Anaesthesia, Westminster Hospital, London*
E. A. COOPER, *Professor of Anaesthesia, University of Newcastle upon Tyne; Honorary Consultant Anaesthetist, Newcastle University Hospitals*
J. W. DUNDEE, *Professor of Anaesthesia, Queen's University of Belfast*
F. R. ELLIS, *Reader in Anaesthesia, University of Leeds*
W. FITCH (Assistant Editor), *Senior Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*
G. M. HALL, *Senior Lecturer in Anaesthetics, University of London, Royal Postgraduate Medical School*
C. J. HULL, *Senior Lecturer in Anaesthesia, University of Newcastle*
A. R. HUNTER (Chairman), *Professor of Anaesthesia, University of Manchester*
D. G. MCDOWALL, *Professor of Anaesthesia, University of Leeds*
W. W. MAPLESON, *Professor of the Physics of Anaesthesia, Welsh National School of Medicine, University of Wales*
J. F. NUNN, *Head of Division of Anaesthesia, Clinical Research Centre, Harrow; Honorary Consultant Anaesthetist, Northwick Park Hospital*
J. P. PAYNE, *British Oxygen Research Professor of Anaesthetics, Royal College of Surgeons of England*
C. PRYS-ROBERTS, *Professor of Anaesthetics, University of Bristol*
J. E. RIDING (Hon. Treasurer), *Consultant Anaesthetist, United Liverpool Hospitals; Honorary Lecturer in the Department of Anaesthesia, University of Liverpool*
J. G. ROBSON, C.B.E. *Professor of Anaesthetics, University of London, Royal Postgraduate Medical School*
D. B. SCOTT, *Consultant Anaesthetist, Royal Infirmary, Edinburgh*
G. SMITH, *Professor of Anaesthesia, The General Hospital, Leicester*
M. K. SYKES, *Professor of Clinical Anaesthesia, Royal Postgraduate Medical School, London*

Editorial Assistants

KIRSTEEN M. S. DEWAR, *Consultant Anaesthetist, Western Infirmary, Glasgow*
G. N. C. KENNY, *Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*

225769
1

Papers for publication and all editorial communications should be addressed to the Editor, University of Glasgow, Department of Anaesthesia, Western Infirmary, Glasgow G11 6NT; business communications to the publishers: Scientific & Medical Division, Macmillan Publishers Ltd, Houndmills, Basingstoke, Hampshire RG21 2XS.

Published monthly. Annual subscriptions: U.K. £22·50, U.S.A. and Canada U.S. $54, Airmail U.S. $120; Rest of World £27 50, Airmail £50; (or equivalent in any other currency). ISSN 0007–0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.

Overseas subscribers may make payments into U.K. Post Office Giro Account No. 519 2455. Full details must accompany the payment.

Second Class Postage Paid New York, N.Y. U.S Mailing Agent: Expediters of the Printed Word, Ltd, PO Box 1305, Long Island City, N.Y. 11101.

All enquiries concerning advertising should be addressed to Advertisement Department, Macmillan Journals Ltd, 3 Dyers Buildings, Holborn, EC1N 2NR (Telephone 01-831 6901). © Copyright: Macmillan Publishers Ltd, 1980. Registered Office: 4 Little Essex Street, London WC2R 3LF

CUR-H05911-3-P25769

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52 SUPPLEMENT 1 1980

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature

INTRODUCTION

The introduction of a new neuromuscular blocking drug into clinical practice is always of great interest, for no two agents in current use are alike and all possess properties which may be undesirable. Experience with those drugs in clinical use gives us a basis to ask sensible questions which will let us predict what will be the value of any new drug.

First, it is essential to know what type of neuromuscular block is produced. Experiments at the junction recording miniature and end-plate potentials are more useful than the easier demonstration that there is fade on tetanic rates of stimulation, post-tetanic potentiation and that the block can be antagonized by anticholinesterase drugs. An assessment of the dissociation constant of the drug will give a good index of its potency and allow it to be compared with other agents. Whole-animal experiments can also assess its potency and the doses likely to be needed in man. The effects of drugs interacting at the neuromuscular junction can also be considered. In man isolated-arm techniques can be used to get a preliminary idea of the human effects in terms of dose, duration of action and the nature of recovery.

Early investigations in man must include studies of the pharmacokinetics associated with the usual methods of administration. Do the blood concentrations following injection show the pattern of a single, double or treble exponential decay? If compartment models can be used, what are their relative volumes and rate constants—or, alternatively, the distribution volumes, α, β and γ half-lives and the clearance? Such studies may also demonstrate the effects of renal and hepatic function on the elimination of the drug.

In addition and, if possible, at the same time it is helpful to relate the concentrations of the drug to the amount of paralysis produced. The isolated-arm technique will show the elimination of effect at low concentrations whilst recovery from bolus i.v. injections will help determine the effect of different doses and repeated injections. Placental transfer also must be studied.

Many neuromuscular blocking drugs affect the autonomic nervous system, having either vagolytic, sympathomimetic or ganglion blocking actions. Animal experiments will help determine the ED_{50} of these effects in relation to the ED_{50} of the neuromuscular block. A large separation suggests that the drug will have significant advantages. The problem of histamine release also needs investigation in animals, although the rare but occasionally fatal anaphylactoid reaction may not be predictable from animal studies.

With such knowledge it should be possible to predict the amounts of drugs needed for patients who need neuromuscular block and what circumstances will alter the intensity and duration of the block. In the 1980's the necessary information can probably be obtained from a small but carefully studied series of patients rather than the hitherto practice of large-scale use which only revealed unwanted effects by accident rather than design.

Such studies will decide the place of a new drug. They also help lay specifications for desirable properties in new agents. Most anaesthetists would prefer agents with few autonomic side-effects. Most would welcome a competitive agent with a rapid onset of action, but may not accept that if it also entails a long duration of action. The relative roles of renal and hepatic elimination and other metabolic pathways need exploration. Perhaps if we are given a short acting, potent, antagonizable agent we may alter our ways of administering blocking drugs. Suxamethonium

LIBRARY

has been given by infusion and there is much interest in continuous i.v. anaesthetic techniques. Perhaps a "clean" short acting, non-cumulative competitive drug will change our current techniques of producing muscle relaxation.

This supplement describes the preliminary findings with Org NC 45, a steroidal agent similar to pancuronium but with only one quaternary nitrogen group. These findings were reported at a meeting in Lucerne in November 1979 organized by Organon-Teknica. We will leave the reader to judge how well its properties are described in terms of what we need to know.

John Norman
W. C. Bowman

Br. J. Anaesth. (1980), **52**, 3S

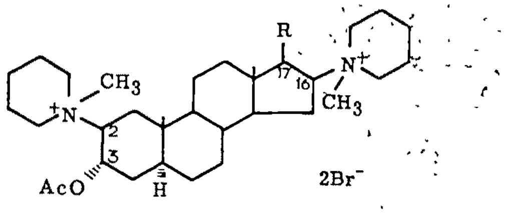
THE EMERGENCE OF ORG NC 45, 1- [(2β,3α,5α,16β,17β)-3, 17-BIS(ACETYLOXY)-2-(1-PIPERIDINYL)-ANDROSTAN-16-YL]-1-METHYLPIPERIDINIUM BROMIDE, FROM THE PANCURONIUM SERIES

D. S. SAVAGE, T. SLEIGH AND I. CARLYLE

SUMMARY

A novel approach is described for obtaining a drug that will be a potent non-depolarizing neuromuscular blocking agent with the potential for a short duration of action and little cumulative effect. This approach led to the discovery of Org NC 45, from the pancuronium series.

In cats, pancuronium bromide (fig. 1) was the most potent member (Buckett, Hewett and Savage, 1973) of a series of non-depolarizing neuromuscular blocking agents (Hewett and Savage, 1965) and the first of the series to be tried in man (Baird and Reid, 1967). Although this drug achieved widespread clinical use, there was still a need for an agent with a shorter time-course of action. Consequently, another member of the same series, dacuronium bromide (fig. 1), which in cats is three to four times shorter in duration of action than its 17-acetoxy derivative pancuronium bromide (fig. 1), was developed for trial in man. Feldman and Tyrrell (1970) and Norman and Katz (1971) showed that the potency and the short time-course of action of dacuronium observed in cats was not borne out in man. A further clinical study (Miller et al., 1978) showed dacuronium bromide to be about one-and-a-half times shorter in duration of action, but 50 times less potent than pancuronium bromide. Working on the hypothesis that a 17-ester group conferred not only potency but also long duration of action, a further analogue, Org 6368, having a hydrogen instead of an oxygen substituent at position 17 (fig. 1) was synthesized (Hewett and Savage, 1974). Again, this was shown to be short-acting and lacking in cumulative effect in cats (Sugrue, Duff and McIndewar, 1975), with a potency five times less than that of pancuronium bromide. This potency ratio was borne out in man (Baird, 1974), but although Org 6368 was faster in onset of action there was little improvement in duration of action.



a) Pancuronium Bromide R =OAc
b) Dacuronium Bromide R = OH
c) ORG 6368 R = H

FIG. 1. Pancuronium bromide and its analogues.

This continued lack of progress led to a reappraisal of current knowledge, since it had become obvious that a different approach was essential if a significant advance was to be made. In 1975 one model of a perfect relaxant was succinctly described by Savarese and Kitz, as a drug having a brief, non-cumulative, non-depolarizing neuromuscular blocking action, with rapid onset and recovery; it should be readily reversible by an appropriate antagonist, cause neither histamine release nor ganglionic blockade, and give rise to minimal cardiovascular side-effects. Coincidentally, it was observed that the various abilities of neuromuscular blocking agents to cause tachycardia in man in clinical doses were receiving increasing attention from both anaesthetists and pharmacologists, and that there seemed to be a correlation between the activities of pancuronium, alcuronium, gallamine and fazadinium in this respect and their abilities to block cardiac muscarinic receptors in cats (Hughes and Chapple, 1976).

D. S. SAVAGE, B.SC., PH.D., A.R.C.S.T., T. SLEIGH, B.SC., PH.D., A.R.C.S.T., F.R.I.C., C.CHEM.; I CARLYLE, B.SC.; Scientific Development Group, Organon Laboratories Limited, Newhouse, Lanarkshire ML1 5SH

0007–0912/80/130003–07 $01.00

© Macmillan Publishers Ltd 1980

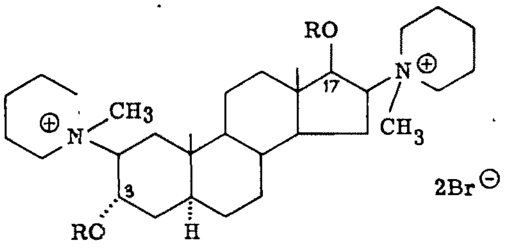
This suggested that drugs could be even more selective in their action than pancuronium, and the whole pancuronium series was reviewed again in this new light.

It has been postulated that a number of physico-chemical factors are associated with the selective action of pancuronium. First, measurement of the inter-atomic distances in conjunction with infra-red and nuclear magnetic resonance data on pancuronium and close analogues allowed the conclusion (Cameron et al., 1970; Savage et al., 1971) that the conformation calculated in the crystal structure approximated to that present at a biological receptor. This was because of the inherent rigidity of the androstane nucleus, which had become even more fixed through the increased steric compression created amongst nuclear substituents by the introduction of the two acetylcholine-like fragments. Furthermore, it was proposed that the geometries and electronic structures within these fragments (Savage et al., 1971), together with the endogenous nature and high degree of asymmetry of the complete molecule (D. S. Savage, 1979*) contribute greatly to the selective pharmacological action of pancuronium.

It was also known (Savage, 1980) that it was possible to carry out several highly selective reactions at different sites in the bis-amino dioxy androstanes related to pancuronium. It is necessary here only to remark that the rates of chemical reactions at various molecular sites in these particular molecules differ sufficiently to confer this selectivity (Kinget and Michoel, 1976).

These considerations formed the basis of our future research. First, the selective chemical reactions allowed the preparation of a planned series of compounds related to pancuronium, having different oxygen substituents at positions 3 and 17, and having different substituents on the nitrogen atoms at positions 2 and 16. Second, and more importantly, they raised the possibility of creating potent drugs of specific chemical structure which might be even more selective for the neuromuscular junction than pancuronium, and which possibly would have significantly altered time-courses of action in man as a consequence of possessing differing susceptibilities to metabolic degradation to less active compounds and differing pharmacodynamic and pharmacokinetic properties at the skeletal muscle nicotinic receptor. In principle then, our plan was to use our knowledge of chemistry of amino steroids to build into our compounds molecular features which might give rise to a drug having a pharmacological profile approximating to that defined for a perfect relaxant by Savarese and Kitz (1975).

The compounds selected were synthesized and tested for neuromuscular and vagal blocking activities in cats anaesthetized with chloralose. Vagal block was tested by determining the ability of a compound to prevent the bradycardia caused by vagal stimulation or by the muscarinic agonist acetyl-β-methylcholine (Durant et al., 1979). A measure of the selectivity of a test drug for the neuromuscular junction was provided by the ratio of the dose producing 50% block of the response to vagal stimulation to that producing 50% twitch depression. This selectivity ratio for pancuronium is 3.4. Hence the target drug, being more selective, will have a significantly greater ratio than 3.4.



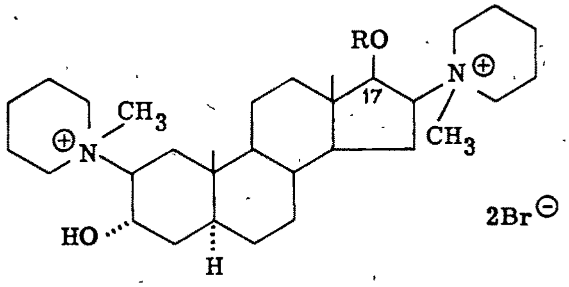
	R	$\frac{V}{N}$
(Pancuronium)	CH_3CO	3.4
	CH_3CH_2CO	6.9
	$CH_3(CH_2)_2CO$	5
	$(CH_3)_2CH_2CO$	2

FIG. 2. The 3,17-diesters and their selectivity ratios (V/N).

The first chemical series examined was the 3,17-diesters (fig. 2), from which it is evident that changing from the diacetate (pancuronium) to longer-chain esters does not alter the selectivity ratio greatly. Maintaining a 3-hydroxyl group and changing the ester group at position 17 demonstrates (fig. 3), by the decreased selectivity ratios, that the drugs become less promising with increasing chain length of the ester. Similarly, replacing

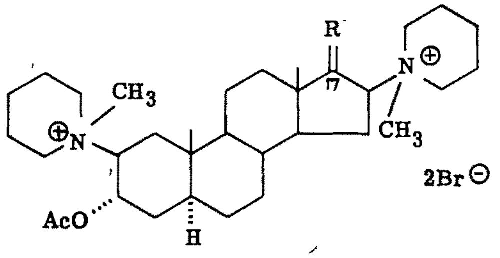
---

* The endogenous nature of pancuronium is associated with the androstane nucleus and two acetylcholine-like molecular fragments; the molecule also contains 10 asymmetric centres. (Presented at the San Francisco meeting on "Present and future clinical uses of muscle relaxants", the proceedings of which are not to be published.)



R	V/N
CH_3CO	4.7
CH_3CH_2CO	0.6
$CH_3(CH_2)_2CO$	0.5
$(CH_3)_2CH_2CO$	0.5
Pancuronium	3.4

FIG. 3. Selectivity ratios (V/N) of analogues retaining a 3-hydroxyl group and changing the ester group at position 17.

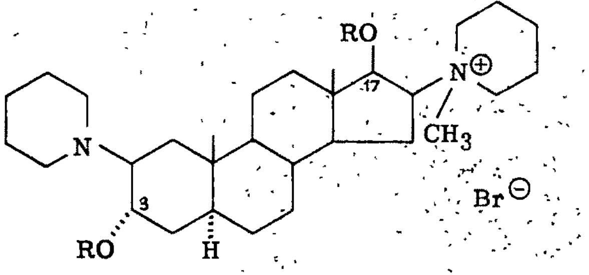


R	V/N
β - OH, α - H	0.7
O	0.8
H, H	1.0
Pancuronium	3.4

FIG. 4. Effect of replacing the 17β-acetoxy group with hydroxyl, hydrogen or 17-keto groups, on selectivity ratio (V/N).

the 17β-acetoxy group of pancuronium with hydroxyl or hydrogen (fig. 4) gives less selective compounds and this is also true for the 17-keto analogue. However, a dramatic improvement was observed in the 17β-acetoxy 16β-monoquaternary series (Durant et al., 1979), the most effective compound being found in the appropriate 3,17-diesters (fig. 5), namely the diacetate, Org NC 45, with a selectivity ratio of 63 compared with the 3.4 of pancuronium.

In addition to being highly selective in action, Org NC 45 is a potent drug, being only 1.6 times less potent than pancuronium in cats (I. G. Marshall and colleagues, 1980, personal communication) which serves to predict that Org NC 45 will be of the same order of activity as pancuronium in man.

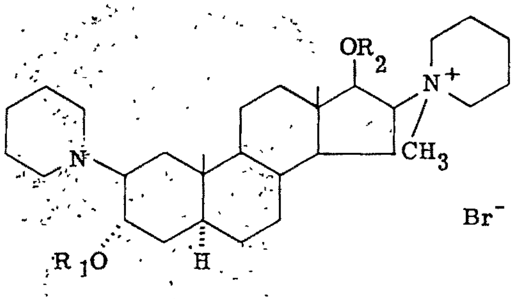


R	V/N
CH_3CO (OrgNC45)	63
CH_3CH_2CO	0.4
$CH_3(CH_2)_2CO$	0.7
$(CH_3)_2CH_2CO$	0.2
Pancuronium	3.4

FIG. 5. One compound in the 17β-acetoxy 16β-monoquaternary series, a 3,17-diester (Org NC 45) has an effective selectivity ratio.

The structure of the molecule is worthy of further comment in terms of medicinal chemistry, and in particular with respect to features which may favourably influence its time-course of action in man. This is important because our previous attempts failed to provide a drug which was significantly quicker in onset and shorter in duration of action in man. Consequently, the novelty of our new approach was to build into the molecule chemical features which could theoretically contribute to this time-course of action in man, in addition to a more selective pharmacological profile.

Comparing the structures of pancuronium bromide (fig. 1) and Org NC 45 (fig. 6), there is one major difference, namely that Org NC 45 lacks the N-methyl group at position 2. As shown earlier (Buckett, Hewett and Savage, 1973), the lack of the second quaternary group does not affect potency, but the second nitrogen atom is essential for high activity. This parallels the monoquaternary, tubocurarine, which has a certain amount of its tertiary nitrogen in the salt form at physiological pH, and hence exists in part as a pseudo bis-quaternary ammonium compound (A. J. Everett, I. A. Lowe and S. Wilkinson, 1971*).



a) Org NC 45 $R_1 = R_2 = Ac$
b) Org 7268 $R_1 = H, R_2 = Ac$
c) Org NC 58 $R_1 = Ac, R_2 = H$
d) Org 7402 $R_1 = R_2 = H$

FIG. 6. Org NC 45 and its metabolites.

It is to be noted that the quaternary ring D acetylcholine fragment of Org NC 45 is always present (unless metabolized), and it has been suggested (Durant et al., 1979) that this specific molecular fragment is intrinsically suited to skeletal muscle nicotinic receptors and is relatively unsuited to cardiac muscarinic receptors.

In addition, there are further chemical subtleties inherent in the Org NC 45 molecule. It was known from earlier work that the ditertiary basic precursor to pancuronium, 2β,16β-diperidino-5α-androstane-3α,17β-diol diacetate, readily deacetylates both in methanolic solution (Gilbert and Savage, unpublished observation) and after i.v. injection into rats (Savage and Sim, unpublished observation). Extraction of the rat plasma after 5 min and analysis of the amino steroid content showed that complete deacetylation had occurred, probably as a result of the neighbouring group effect of the tertiary basic 2β- and 16β-nitrogens on the 3- and 17-oxygen functions (cf. Hewett and Savage, 1968). Therefore it is reasonable to expect that 3-acetate groups in Org NC 45 molecules in which the 2β-nitrogen is tertiary will most readily deacetylate independent of cholinesterase to the 3α-ol at physiological pH 7.4. Animal experiments predict that this 3α-ol derivative (Org 7268) (fig. 6) is as potent as Org NC 45 in man, that both drugs have a faster rate of recovery than pancuronium, and that Org NC 45 is the fastest in this respect (Durant et al., 1979).

This fast rate of recovery prompted studies on comparative stability amongst the bis-quaternary pancuronium, its major metabolite (the 17-monoacetate-Org NE 35), and the monoquaternary Org NC 45 and its corresponding major metabolite (the 17-monoacetate Org 7268). Interestingly, both bis-quaternary compounds proved relatively stable in aqueous solution over 6 h at 20 °C, in contrast to Org NC 45 and Org 7268 which showed significant conversion by deacetylation after only 0.5 h to Org 7268 and the diol, Org 7402 (fig. 6) respectively. This could prove to be of extreme importance because the diol (Org 7402), which is presumably the terminal metabolite, is 60 times less potent in cats than is Org NC 45 (Durant et al., 1979). This suggests that Org NC 45 is liable to chemical conversion to relatively inactive metabolites at a rate which promotes a faster recovery from neuromuscular block than is observed with pancuronium. This does not exclude the possibility of metabolic degradation. Consequently it is reasonable to expect that Org NC 45 will have a significantly shorter duration of action in man than pancuronium. Since the more rapid recovery is chemically dependent, it is to be expected also that the process can be repeated reliably and consistently in man, thereby minimizing problems with respect to prolonged neuromuscular block and cumulation.

Finally, with respect to onset and duration of action, rate of recovery, distribution and elimination of Org NC 45, it is of interest to mention briefly some data on solubility properties of some non-depolarizing drugs and the probable characteristics of Org NC 45. Both bis-quaternaries, pancuronium (3,17-diacetate) and its metabolite dacuronium (3-acetate 17-ol), dissolve readily in 5 volumes of methylene dichloride (CH_2Cl_2), unlike the terminal metabolite (3,17-diol) and the monoquaternary, tubocurarine, which are virtually insoluble in 20 volumes of methylene dichloride. All four drugs enter the aqueous phase almost entirely when partitioned between methylene dichloride and water. None of the four drugs is soluble in diethyl ether to any significant extent, neither is Org NC 45, unlike the precursor common to both pancuronium and Org NC 45, which has no quaternizing N-methyl groups. In general therefore, it can be surmised that, although the monoquaternary Org NC 45 is hydrophilic, it will be relatively more lipophilic than the bis-quaternary pancuronium, its metabolites and the phenolic mono-quaternary, tubocurarine. Indeed, Org NC 45 does not dissolve in water as readily as pancuronium, although the rate of solution does increase with decreasing pH and concomitant protonation of the tertiary 2β-N atoms, which explains the ready solution of Org NC 45, when added to the aqueous, acid buffer solution employed in the pharmaceutical formulation.

---

* Revision of the structures of (+)-tubocurarine and (+)-chondocurine. (Unpublished observation from lecture "Recent developments in anaesthetic and neuromuscular blocking drugs" at the Society for Drug Research.)

In summary, the data presented in this paper suggest that Org NC 45 will prove to represent an advance with respect to being a potent, non-depolarizing, neuromuscular blocking agent with minimal cardiovascular side-effects. It remains to be determined to what extent the other latent subtleties, described in terms of the inherent chemical properties of Org NC 45, contribute to significant improvements in time course of action and lack of cumulative effect.

ADDENDUM

THE PHARMACEUTICAL FORMULATION OF ORG NC 45*

Extensive pharmaceutical studies with Org NC 45, a myoneural blocking agent, reveal that the compound is liable to deacetylate in aqueous solution over a wide range of pH. This deacetylation occurs most readily at position 3 of the molecule. A ready-for-use aqueous preparation could not be prepared because it is unstable; therefore a buffered lyophilized product, which is stable, has been developed. It is easily reconstituted in water for i.v. administration. Critical factors in the manufacture of a chemically stable lyophilized preparation have proved to be the pH of the solution to be lyophilized; and the residual moisture content in the lyophilized cake.

Each ampoule contains 4 mg of Org NC 45, a citrate–phosphate buffer to obtain both an optimum pH in the solution to be lyophilized and to protect the active principle in the lyophilized cake against attack from residual moisture and mannitol to act as a carrier and also to obtain an isotonic solution after reconstitution with 1 ml of water for injection. The composition of the cake is: Org NC 45 4.0 mg, citric acid 8.3mg, disodium phosphate 6.5 mg, mannitol 24.5 mg. All subsequent data are based on this standard composition.

Manufacture

Org NC 45 is dissolved in an aqueous solution previously buffered at a pH of 4. This solution is sterilized by membrane filtration, aseptically filled into ampoules, and lyophilized immediately. One millilitre of water for injection is added for reconstitution according to this formula.

The stabilizing effect of this buffer system depends on two physico-chemical phenomena:

(1) The buffer system maintains a pH of 4 in the aqueous solution of Org NC 45, since it has been shown that this is the optimum pH for stability, albeit limited.

(2) Disodium phosphate possesses the intrinsic ability to bind 2–7 molecules of water. Incorporation of disodium phosphate is sufficient to bind strongly the residual content of free moisture still present after freeze-drying and subsequent closing of the ampoules. Consequently the vapour pressure of water in the ampoule is reduced to such a level that the active compound Org NC 45 is protected against degradation of its acetoxy groups.

This choice of lyophilized preparation for Org NC 45 and carefully controlled manufacture procedure makes it possible to introduce a product with a shelf-life of at least 2 years.

Stability

Stability of the reconstituted solution. Stability studies on aqueous solutions of Org NC 45 containing 4 mg ml^{-1} prepared from the corresponding lyophilized cake, show that the reconstituted solutions are sufficiently stable for use within 1 day (table I).

TABLE I. *Stability of the reconstituted Org NC 45 when stored at various conditions*

Storage period/conditions	Decomposition (%)
Zero-time	1–2
1 day: 4 °C	1–2
25 °C (dark)	1–2
25 °C (daylight)	1–2

Stability of lyophilized cake in ampoules Several batches of lyophilized Org NC 45 formulations of the standard composition were subjected to stability testing. Quantitative, semi-quantitative and qualitative chemical assays and physical assessment indicate a shelf-life for the preparation of at least 2 years when stored at room temperature in the dark. As an example the stability data of two batches are given in table II.

Various batches of lyophilized Org NC 45 preparations were assessed for appearance and dissolution characteristics of the cake, and after reconstitution for clarity, colour and pH of the solution obtained.

Upon storage under various conditions (up to 45 °C for 1 yr) no statistically significant changes were observed with respect to data obtained at zero-time.

Analytical methods

The content of Org NC 45 in the lyophilized preparation is determined according to a specific and reproducible high-performance liquid chromatographic procedure which is accurate to within 2%. Identification of Org NC 45, detection and semi-quantitative estimation of decomposition products are carried out by thin-layer chromatography.

Physical assessment is performed by visual inspection on appearance of the cake, dissolution characteristics and on clarity and colour of the reconstituted solution, using the European Pharmacopoeia requirements for injectables as reference.

---

* H. BURGER; J. EGBERINK; J. LAKEMAN; Organon International B.V., Pharmaceutical R & D Labs., Oss, The Netherlands.

TABLE II. *(Semi)-quantitative assay of lyophilized Org NC 45 (4 mg per ampoule) after storage periods up to 1 year. *Percentage of declaration; †Percentage of content of active principle; — not determined; – – not yet available*

	Org NC 45*		Decomposition products†	
Storage period and conditions	Batch 411/78	Batch 09.4338.105	Batch 411/78	Batch 09.4338.105
Zero-time	—	99	—	1
3 months				
4 °C	99	98	1	1
25 °C	99	100	1.5	1
37 °C	99	98	1.5	1
45 °C	98	96	3	1.5
6 months				
4 °C	104	100	1	1
25 °C	100	102	1	1
37 °C	99	100	2.5	1.5
45 °C	—	100	—	2
12 months				
4 °C	107	– –	1	– –
25 °C	107	– –	2	– –
37 °C	106	– –	3	– –
45 °C	100	– –	4	– –

Compatibility with infusion fluids

Reconstituted Org NC 45 may have to be administered by infusion during prolonged operations. Consequently, its physical and chemical compatibility have been investigated at a concentration of 40–100 mg $litre^{-1}$ in 0.9% NaCl (5%) glucose, Ringer's Lactate and in Ringer's–glucose infusion fluids. The infusion fluids tested were packed both in glass infusion bottles and in p.v.c. bags. The compatibility studies showed that the infusion solutions were chemically and physically stable for 24 h when stored at room temperature and in normal daylight.

ACKNOWLEDGEMENTS

The authors extend their gratitude to Mrs G. Kruyt-Lovink, Miss G. Tenkink, Miss I. Mentink, Mr J. Vos and Mr J. van Harskamp for their scientific contribution and technical assistance.

REFERENCES

Baird, W. L. M (1974). Initial studies in man with a new myoneural blocking agent (Org 6368). *Br. J. Anaesth.*, **46**, 658.

—— Reid, A. M. (1967). The neuromuscular blocking properties of a new steroid compound, pancuronium bromide; a pilot study in man. *Br. J. Anaesth.*, **39**, 775.

Buckett, W. R., Hewett, C. L , and Savage, D. S. (1973). Pancuronium bromide and other steroidal neuromuscular blocking agents containing acetylcholine fragments. *J Med Chem.*, **16**, 1116.

Cameron, A. F., Ferguson, G., Buckett, W. R., Hewett, C L., and Savage, D. S. (1970). The use of physical chemistry (x-ray crystallography, IR and NMR) to determine possible receptor site conformation of pancuronium bromide. *VI Rencontr. Chim. Ther.*, Brussels, 1970

Durant, N. N., Marshall, I. G., Savage, D. S., Nelson, D. J., Sleigh, T., and Carlyle, I C. (1979). The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45, and other pancuronium analogues, in the cat. *J. Pharm. Pharmacol.*, **31**, 831

Feldman, S. A., and Tyrrell, M. F. (1970). NB68. A new steroid muscle relaxant. *Anaesthesia*, **25**, 349.

Hewett, C. L., and Savage, D. S. (1965). 2β,16β-Diamino-androstanes. British Patent 1,138,605.

—— —— (1968). Amino steroids. Part III. 2- and 3-Amino-5α-androstanes, *J. Chem. Soc.* (C), 1134.

—— —— (1974). 2β,16β-Diamino-5α-androstanes. British Patent 1,454,749.

Hughes, R. M., and Chapple, D J. (1976). Effects of non-depolarizing neuromuscular blocking agents on peripheral autonomic mechanisms in cats. *Br J. Anaesth.*, **48**, 59.

Kinget, R., and Michoel, A (1976). Kinetic study of the hydrolysis of pancuronium bromide. *Acta Pharm. Suec.*, **13**, 321.

Miller, R. D., Agoston, S., Booij, L. H. D. J., Kersten, U. W., Crul, J. F., and Ham, J. (1978). The comparative potency and pharmacokinetics of pancuronium and its metabolites in anaesthetised man. *J. Pharmacol. Exp Ther.*, **207**, 539.

Norman, J., and Katz, R. L. (1971). Some effects of the steroidal muscle relaxant, dacuronium bromide, in anaesthetized patients. *Br. J. Anaesth.*, **43**, 313.

Savage, D. S. (1980). Mechanisms of action of muscle relaxants and relationships between structure and activity; in *Curares and Curarization*, p. 21 Paris: Librairie Arnette; Amsterdam: Excerpta Medica. (Also available in a French edition.)

—— Cameron, A. F., Ferguson, G., Hannaway, C., and Mackay, I. R. (1971). Molecular structure of pancuronium bromide (3α,17β-diacetoxy-2β-dipiperidino-5α-androstane dimethobromide), a neuromuscular blocking agent. Crystal and molecular structure of the water: methylene chloride solvate. *J. Chem. Soc.* (B), 410.

Savarese, J. J., and Kitz, R. J. (1975). Does clinical anesthesia need new neuromuscular blocking agents? *Anesthesiology*, 42, 236.

Sugrue, M. F., Duff, N., and McIndewar, I. (1975). On the pharmacology of Org6368 (2β,16β-dipiperidino-5α-androstan-3α-ol acetate dimethobromide), a new steroidal neuromuscular blocking agent. *J. Pharm. Pharmacol.*, 27, 721.

EMERGENCE D'ORG NC 45, 1-[(2β,3α,5α,16β,17β)-3,17-BIS(ACETYLOXY)-2-(1-PIPERIDINYL)-ANDROSTAN-16-YL]-1-BROMURE DE METHYLPIPERIDINIUM, DE LA SERIE DES PANCURONIUM

RESUME

On décrit dans cet article une nouvelle manière de procéder pour obtenir un médicament qui sera un agent de blocage neuromusculaire puissant et non dépolarisant dont le potentiel sera une courte durée d'action et peu d'effets cumulatifs. Cette manière de procéder a permis de découvrir Org NC 45 dans la série des pancuronium.

DAS AUFTAUCHEN VON ORG NC 45, 1-[(2β,3α,5α,16β,17β)-3,17-BIS(ACETYLOXYD)-2-(1-PIPERIDINYL)-ANDROSTAN-16-YL]-1-3 METHYLPIPERIDINIUMBROMID, AUS DER PANCURONIUM-REIHE

ZUSAMMENFASSUNG

Beschrieben wird ein neuartiger Weg zur Erzielung einer Droge, die ein starkes, nicht-depolarisierendes, neuromuskuläres Blockierungsmittel ist, mit einem Potential für kurze Wirkungsdauer und geringem kumulativem Effekt. Dieser neue Weg führte zu der Entdeckung von Org NC 45 aus der Pancuronium-Reihe.

OBTENCION DEL ORG NC 45, 1-[(2β,3α,5α,16β, 17β)-3,17-BIS(ACETILOXIA)-2-(1-PIPERIDINILO)-ANDROSTAN-16-ILO]-1-BROMURO DE PIPERIDINIUM DE METILO, A PARTIR DE LA SERIE PANCURONIUM

SUMARIO

Descripción de un nuevo procedimiento de obtención de una droga que será un potente agente no despolarizante de bloqueo neuromuscular, con el potencial para que su acción sea de corta duración y su efecto acumulativo sea pequeño. Este procedimiento llevó a descrubrir el Org NC 45 partiendo de la serie pancuronium.

Br. J. Anaesth. (1980), 52, 11S

PHARMACOLOGY OF ORG NC 45 COMPARED WITH OTHER NON-DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

I. G. Marshall, S. Agoston, L. H. D. J. Booij, N. N. Durant and F. F. Foldes

SUMMARY

From results of pharmacological tests on the neuromuscular and autonomic blocking actions of a series of pancuronium analogues, Org NC 45, the C16 monoquaternary analogue of pancuronium, was selected for detailed study. Org NC 45 has a non-depolarizing mechanism of action, is more rapid in onset and shorter in duration of action than pancuronium. It shows less cumulation than pancuronium or tubocurarine, and is easily antagonized by anticholinesterases and aminopyridines. Org NC 45 exhibits a low propensity to release histamine. Its ability to inhibit cholinesterases is not likely to be important at neuromuscular blocking doses. Org NC 45 possesses negligible ganglion-blocking activity and there is a wide margin between neuromuscular and vagal blocking doses. Thus cardiovascular side-effects are unlikely to occur with the use of Org NC 45. It will hydrolyse mainly to its 3-hydroxy analogue which, like Org NC 45, possesses a wide margin between neuromuscular and vagal blocking doses. Org NC 45 has a high selectivity for the neuromuscular junction and represents a potentially useful addition to the armamentarium of clinically useful muscle relaxants.

The synthesis and pharmacology of monoquaternary 2β,16β-dipiperidino-3α,17β-diacetoxy-5α-androstanes was first described by Buckett, Hewett and Savage (1973). The most potent of the monoquaternary compounds, Org NC 45, was shown to have about one-half to two-thirds of the potency and duration of action of the corresponding bisquaternary compound, pancuronium bromide, in the cat (Marshall, 1968; Buckett, Hewett and Savage, 1973) and in the fowl (Marshall, 1968). In preliminary experiments, little cumulation was seen on repeated administration and recovery following i.v. infusion. The compound blocked the response to close-arterially injected acetylcholine and its neuromuscular blocking action was readily antagonized by neostigmine. The block was enhanced when the stimulation frequency was increased from 0.1 Hz to 1 Hz, but no prolonged block of the hemicholinium type occurred. These results indicated that the block was mainly postjunctional in nature and was of a non-depolarizing type (Marshall, 1968). With the knowledge available at the time, no striking advantages of Org NC 45 were realized; furthermore, the compound was unstable in aqueous solution. Further work on it at that time was abandoned.

Since the early studies on the pancuronium series, the importance of cardiovascular side-effects of neuromuscular blocking agents has become apparent. Accordingly, a series of analogues of pancuronium, including Org NC 45, was tested for both neuromuscular and autonomic blocking activities (Durant et al., 1979). Org NC 45 was selected for further study from this series on the grounds that it was the compound most likely to be capable of producing neuromuscular block without concomitant cardiovascular side-effects. Its development and chemical properties and the means of overcoming its instability in aqueous solution are discussed by Savage in this supplement (Savage, Sleigh and Carlyle, 1980).

Neuromuscular blocking action

In the isolated chick biventer cervicis nerve–muscle preparation, Org NC 45 produced a depression of indirectly elicited twitch responses and of responses to added acetylcholine without a concomitant contracture of the multiple innervated fibres (Durant et al., 1979). This observation

---

I. G. Marshall, ph.d.; N. N. Durant,* ph.d.; Department of Physiology and Pharmacology, University of Strathclyde, Glasgow G1 1XW. S. Agoston, m.d., ph.d., Departments of Clinical Pharmacology and Anesthesiology, State University of Groningen, Groningen, The Netherlands. L. H. D. J. Booij, m.d., Institute of Anesthesiology, Catholic University of Nijmegen, Nijmegen, The Netherlands. F. F. Foldes, m.d., Department of Anesthesiology, Montefiore Hospital and Medical Center and Albert Einstein College of Medicine, Bronx, N.Y. 10467, U.S.A.

* Present address: Department of Anesthesiology, Center for the Health Sciences, University of California at Los Angeles, Los Angeles, Ca 90024, U.S.A.

0007-0912/80/130011-09 $01.00

© Macmillan Publishers Ltd 1980

TABLE I. *Potencies and time-courses of action of Org NC 45 and pancuronium in anaesthetized rats, cats, dogs and monkeys.* **Time to 50% recovery with* $3 \times ED_{90}$ *dose*

Species, anaesthetic and muscle	Drug	Dose to produce about 90% twitch block	Mean block (%)	Time from injection to max block (min)	Time from injection to 90% recovery (min)	Recovery time from 25% to 75% control twitch (min)	References other than present study
Rat Sodium pentobarbitone Tibialis anterior	Org NC 45	250 $\mu g\ kg^{-1}$	88±3.1	1.17±0.15	3.3±0.6	0.9±0.2	
	Pancuronium	100 $\mu g\ kg^{-1}$	84.7±11.6	1.4±0.1	9.1±3.8	2.6±1.1	
Cat α-Chloralose Gastrocnemius	Org NC 45	38 $\mu g\ kg^{-1}$	85.2±2.6	4.72±0.25	8.18±0.58	1.9±0.24	I. McIndewar (unpublished)
	Pancuronium	24 $\mu g\ kg^{-1}$	84.1±2.0	5.93±0.21	12.12±0.93	3.06±0.33	
Rhesus monkey Ketamine–sodium pentobarbitone–nitrous oxide Adductor pollicis	Org NC 45	10 $\mu g\ kg^{-1}$	82.4±5.5	7.8±0.6	20.4±1.6	6.6±0.6	Durant, Houwertjes and Crul (1980)
	Pancuronium	7 $\mu g\ kg^{-1}$	79.5±2.5	7.3±1.3	22.4±5.4	8.8±2·5	
Dog Halothane Hind limb extensors	Org NC 45	14 $\mu g\ kg^{-1}$			42±2*		Booij and others (1980)
	Pancuronium	22 $\mu g\ kg^{-1}$			108±10*		

confirms that the block is of a non-depolarizing nature and is postjunctional in origin.

The neuromuscular blocking action of Org NC 45 has been tested in largely unpublished experiments on rats, cats, dogs and monkeys by several groups of workers (in Glasgow, Groningen, and Nijmegen) and its actions have been compared where appropriate with those of pancuronium and of other neuromuscular blocking drugs. Table I compares the potency of and time-course of the effects of Org NC 45 with those of pancuronium in the above four species.

The results show that Org NC 45 is of the same order of potency as pancuronium, being somewhat more potent in the dog and somewhat less potent in the other three species. Its onset of action (time from injection to maximum effect) is slightly more rapid than that of pancuronium (e.g. about 1.3 times more rapid in the cat) and its duration of action (time from injection to 90% recovery) and recovery (time of recovery from 25% to 75% control twitch height) are substantially shorter than those of pancuronium. When the same dose of Org NC 45 (0.25 $mg\ kg^{-1}$) was repeatedly injected into anaesthetized rats, the second and subsequent doses being administered at the time of full recovery of the twitches after the preceding dose, there was a small degree of cumulation between the first and second doses, but the effects of subsequent doses were essentially the same. Cumulation was more marked with successive doses of pancuronium and was still more pronounced when tubocurarine was the blocking agent used. The histograms of figure 1 illustrate the depths and durations of successive blocks produced by tubocurarine, pancuronium and Org NC 45.

Similar results were obtained in anaesthetized cats. Thus, when a dose of Org NC 45 (35 $\mu g\ kg^{-1}$) sufficient to produce 80–90% twitch block of the gastrocnemius muscle was injected repeatedly, each dose being administered at the time of full recovery from the preceding dose, there was little or no cumulation as illustrated in figure 2. In contrast, pancuronium, and especially tubocurarine, were strongly cumulative.

Reversal by anticholinesterases and by aminopyridines

Reversal of the neuromuscular block produced by Org NC 45 has been assessed by two types of experiment. In one type of experiment the re-

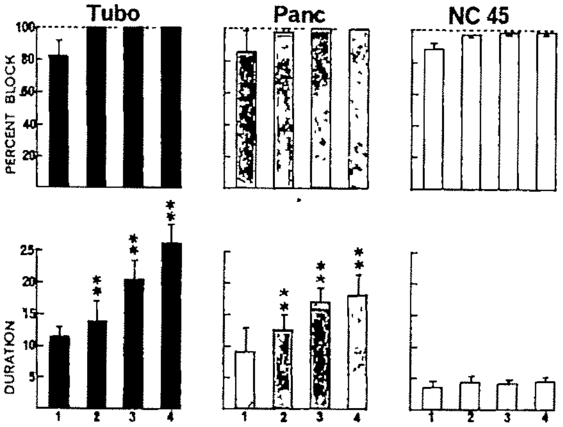


FIG. 1. Repeated doses of tubocurarine 0.08 mg kg^{-1}, pancuronium 0.1 mg kg^{-1} or Org NC 45 0.25 mg kg^{-1} were administered to rats under sodium pentobarbitone anaesthesia and the depths and durations (time from injection to 90% recovery) of the neuromuscular blocks produced in the tibialis anterior muscle (stimulated through its nerve at 0.1 Hz) were noted. Only one drug was administered to any one rat. Each dose was injected at the time of complete recovery from the preceding dose. Each drug was studied in six rats. **Significant difference from block produced by first dose ($P < 0.01$).

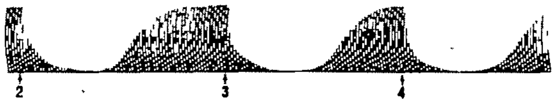


FIG. 2. Tibialis anterior muscle–sciatic nerve preparation of the chloralose-anaesthetized cat; stimulation frequency 0.1 Hz. The effects of the second, third and fourth doses of a series of successive administrations of Org NC 45 40 μg kg^{-1}. Note the lack of cumulative effects with successive doses

covery time from 25% to 75% of control twitch height, after an approximately 90% blocking dose of neuromuscular blocking agent, has been assessed before and after the injection of the reversal agent. For example, in four cats, Org NC 45 40 μg kg^{-1} produced a neuromuscular block in which the time from 25% to 75% recovery was 2.1 ± 0.3 min. Neostigmine 70 μg kg^{-1} injected at the peak of the neuromuscular block reduced this time to 0.98 ± 0.2 min. Similar results were obtained in rats and dogs.

In another study using this type of analysis Durant, Houwertjes and Crul (1980) have compared the abilities of anticholinesterases and aminopyridines to reverse pancuronium- and Org NC 45-induced neuromuscular blockades in the anaesthetized rhesus monkey (table II).

In the second type of experiment, the neuromuscular blocking drugs were infused i.v. into

TABLE II. *Effects of anticholinesterases and aminopyridines on recovery (from 25 to 75% control twitch height) from pancuronium and Org NC 45-induced neuromuscular blockade in the anaesthetized monkey ulnar nerve–adductor pollicis muscle preparation*

Reversal agent	Dose	Recovery time (min)	
		Pancuronium	Org NC 45
Control	—	12.3 ± 1.7	7.1 ± 0.5
Neostigmine	35 μg kg^{-1}	3.9 ± 0.9	3.8 ± 0.8
Pyridostigmine	105 μg kg^{-1}	8.8 ± 2.0	3.9 ± 0.7
4-Aminopyridine	1 mg kg^{-1}	4.4 ± 2.1	5.2 ± 0.7
3,4-Aminopyridine	1 mg kg^{-1}	3.5 ± 0.2	2.9 ± 1.0

TABLE III. *Comparison of the doses (μg kg^{-1}) of neostigmine, pyridostigmine and 4-aminopyridine alone or in combination required to produce 50% antagonism of pancuronium or Org NC 45-induced neuromuscular block in the anaesthetized rat (From Booij et al.,* 1980)

Reversal agent	Pancuronium	Org NC 45
Neostigmine (Neo)	18	14.5
Pyridostigmine (Pyr)	49	75
4-Aminopyridine (4-AP)	440	466
Neo + 4-AP (100 μg kg^{-1})	7.4	9.8
Pyr + 4-AP (200 μg kg^{-1})	11	18
4-AP + Neo (3.5 μg kg^{-1})	220	215
4-AP + Pyr (25 μg kg^{-1})	76	130

anaesthetized rats until a steady state 90% block of twitch height was achieved. Reversal agents, either singly or combined, were then injected as an i.v. bolus with the infusion continuing. In this way dose-antagonism plots can be obtained and doses of antagonists producing 50% reversal can be calculated (Miller et al., 1978). By means of this technique it has been shown that neostigmine, pyridostigmine and 4-aminopyridine are effective antagonists of both pancuronium- and Org NC 45-induced neuromuscular block and that the anticholinesterases interact with 4-aminopyridine in a synergistic manner (Miller et al., 1978; Booij et al., 1980) (table III).

Unwanted effects of non-depolarizing neuromuscular blocking drugs

The main unwanted effects of various non-depolarizing blocking agents in current clinical use are (i) release of histamine and other autacoids, (ii) anticholinesterase activity, (iii) autonomic ganglion block, (iv) block of cardiac vagus neuroeffector transmission and of muscarinic receptors on noradrenergic nerve endings, (v) inhibition of neuronal noradrenaline re-uptake and possibly stimulation of noradrenaline release.

In addition, potency may be modified by the pH of the extracellular fluids and by body temperature. The drugs are likely to interact with some of the various anaesthetics and adjuvants to anaesthesia used concurrently, and possibly with other medication taken by the patient. Cardiovascular effects of Org NC 45 are the subject of the paper by Marshall and colleagues (1980) in this supplement, and its interactions with other drugs are described by Krieg and colleagues (1980), also in this supplement. Here we confine ourselves to dealing with items (i), (ii) and (iii) listed above, and with the ability of neuromuscular blocking drugs to block the cardiac vagus in the cat.

(i) *Histamine release.* Tubocurarine provides the main example of a neuromuscular blocking drug that releases histamine. The effect is relatively unimportant with the other drugs in current use. The matter has been reviewed by MacLagan (1976).

Arterial pressure, heart rate, transpulmonary pressure, rate of airflow and tidal volume were recorded simultaneously with maximal twitches of a tibialis anterior muscle (0.1 Hz) in artificially ventilated cats under chloralose anaesthesia (I. W. Rodger, personal communication). Tubocurarine in a dose sufficient to produce about 90% block of the twitches (0.4 mg kg^{-1}) caused a decrease in arterial pressure, a reflex increase in heart rate, and usually a slowly developing increase in transpulmonary pressure without change in rate of airflow or tidal volume (Gandiha et al., 1975). A similar increase in transpulmonary pressure was produced by a small dose of histamine, and may be attributed to constriction of alveolar ducts and respiratory bronchioles. The effect of histamine and the effect of tubocurarine on transpulmonary pressure were blocked by mepyramine 0.5 mg kg^{-1}. Part of the decrease in arterial pressure produced by tubocurarine was also blocked by mepyramine. The mepyramine-sensitive effects of tubocurarine on arterial pressure and transpulmonary pressure may be attributed to histamine release.

Neither pancuronium nor Org NC 45 in doses up to three times those necessary to produce 90% twitch block (the maximum doses used) produced any evidence of histamine release in Rodger's experiments. Figure 3 illustrates the absence of effect of Org NC 45 on respiratory parameters.

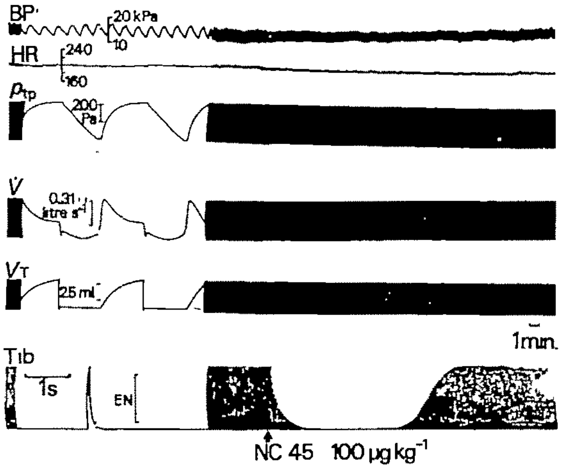


FIG 3. Chloralose-anaesthetized cat. Effects of a neuromuscular blocking dose of Org NC 45 on arterial pressure (BP), heart rate (HR), transpulmonary pressure (p_{tp}), rate of airflow ($\dot{V}$), tidal volume (V_T) and responses of the tibialis anterior muscle to sciatic nerve stimulation (Tib). In a dose producing a similar depth of neuromuscular block tubocurarine causes an increase in transpulmonary pressure as a result of release of histamine Note that no such increase was produced with Org NC 45. (Figure supplied by Dr I. W. Rodger and Professor W. C. Bowman.)

In human volunteers, the ability of Org NC 45 to release histamine was compared with that of pancuronium, metocurine and tubocurarine (L. H. D. J. Booij, N. Krieg and J. F. Crul, unpublished data). Intradermal injections of equiactive neuromuscular blocking doses of the compounds produced skin redness and induration. Tubocurarine and metocurine produced the largest diameters of redness and induration; pancuronium came next in order. Org NC 45 produced by far the smallest area of redness and induration.

Thus, in both experimental animals and human volunteers Org NC 45 produced less evidence of histamine release than any of the other muscle relaxants tested.

(ii) *Cholinesterase inhibition.* From the point of view of their inhibitory effect on human red cell acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BuChE), the non-depolarizing neuromuscular blocking agents may be divided into three sub-groups. The members of the first sub-group, tubocurarine, metocurine, alcuronium and gallamine, are relatively weak inhibitors of both AChE and BuChE and there is no great difference between their inhibitory effect on the two types of enzymes (table IV). The lone member of the second sub-group, benzoquinonium, is a potent inhibitor of AChE and is a 100-times more potent inhibitor of this enzyme than of BuChE.

TABLE IV. *The inhibitory effect of neuromuscular blocking agents on the hydrolysis of acetylcholine by human red cell acetylcholinesterase (AChE) and plasma butyrylcholinesterase (BuChE).* **I_{50} = concentration of relaxant producing* 50% *reduction in rate of hydrolysis.* †*Source of enzyme washed human red cell; substrate concentration* 3.1 *mol litre*$^{-3}$. ‡*Source of enzyme purified human plasmacholinesterase, substrate concentration* 2.2 *mol litre*$^{-2}$

Neuromuscular blocking agent	I_{50} (mol litre^{-1})* AChE†	I_{50} (mol litre^{-1})* BuChE‡	I_{50} AChE / I_{50} BuChE
d-Tubocurarine	7.2×10^{-4}	3.0×10^{-4}	2.4
Metocurine	3.2×10^{-3}	4.8×10^{-4}	6.6
Alcuronium	6.7×10^{-4}	5.4×10^{-5}	12.4
Gallamine	4.5×10^{-4}	2.4×10^{-4}	1.9
Benzoquinonium	2.2×10^{-7}	2.1×10^{-5}	0.01
Pancuronium	3.0×10^{-4}	5.6×10^{-8}	4838.7
Org NC 45	6.6×10^{-5}	6.2×10^{-7}	106.4

The members of the third sub-group, pancuronium and to a lesser extent Org NC 45, are potent inhibitors of BuChE. Pancuronium and Org NC 45 respectively inhibit BuChE at concentrations about 5000 and 100 times less than those required to inhibit AChE.

Because of its high AChE inhibitory potency, the administration of neuromuscular blocking doses of benzoquinonium may be accompanied by severe muscarinic side-effects such as circulatory collapse. For this reason its clinical use has been abandoned.

Inhibition of BuChE by pancuronium has important theoretical considerations, as it would be expected that pancuronium would prolong the action of drugs, such as procaine, that are dependent upon BuChE-mediated hydrolysis for the termination of their action. Since the BuChE-inhibitory potency of Org NC 45 is about 10 times less than that of pancuronium, prolongation of the effects of such drugs is less likely to occur after the preliminary administration of Org NC 45.

(iii) *Ganglion block.* Sympathetic ganglion block produced by tubocurarine and fazadinium contributes to the hypotension seen in man with these agents (McDowell and Clarke, 1969; Blogg et al., 1973; Ungerer and Erasmus, 1974).

Neither pancuronium nor Org NC 45 produces ganglion block at neuromuscular blocking doses as assessed by measuring responses of the anaesthetized cat nictitating membrane preparation to preganglionic cervical sympathetic nerve stimulation (Buckett et al., 1968; Durant et al., 1979). The absence of effect of a neuromuscular blocking dose of Org NC 45 on responses of the nictitating membrane to preganglionic stimulation is illustrated in figure 4.

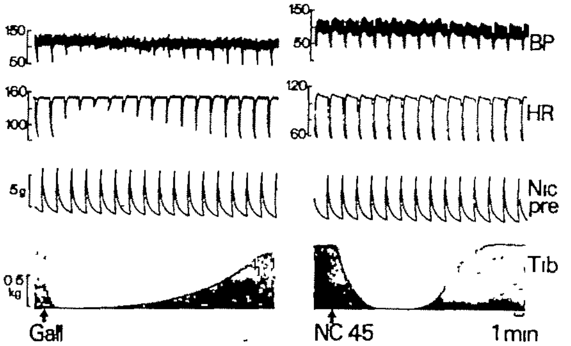


FIG. 4. Effects of gallamine (Gall) 0 8 mg kg^{-1} and, in a different experiment, Org NC 45 40 µg kg^{-1} on arterial pressure (BP) (mm Hg), heart rate (HR) (beat min^{-1}), contractions of the nictitating membrane (Nic pre) in response to preganglionic stimulation (5 Hz for 5 s every 100 s), and maximal twitches of a tibialis anterior muscle (Tib) evoked by stimulation of its motor nerve (0.1 Hz). The right vagus was stimulated every 100 s for 5 s at 8 Hz to evoke decreases in heart rate (and consequently in arterial pressure) In a dose just sufficient to produce 100% twitch block, gallamine inhibited the cardiac vagus, but Org NC 45 did not. Neither drug affected the responses of the nictitating membrane (From Bowman, 1980.)

(iv) *Blockade of cardiac vagus neuroeffector transmission.* Neuromuscular blocking doses of gallamine, pancuronium, alcuronium and fazadinium can cause tachycardia in man (Smith and Whitcher, 1967; Kennedy and Kelman, 1970; Kelman and Kennedy, 1971; Blogg et al., 1973). Gallamine and pancuronium have been studied in detail and have been found to have atropine-like actions that are confined to the cardiac vagus neuroeffector junction (Riker and Wescoe, 1951; Saxena and Bonta, 1970). Thus atropine itself will block both the bradycardia and the vasodilator action of the muscarinic agonist acetyl β-methylcholine, whereas drugs that selectively block the cardiac receptors block only the bradycardial response, leaving the vasodilator response intact.

The anaesthetized cat has very little spontaneous vagal tone, but blockade of cardiac vagus neuroeffector transmission may be conveniently measured by assessing the antagonism of the

TABLE V *Neuromuscular and vagal blocking activities of Org NC 45 compared with those of clinically used non-depolarizing neuromuscular blocking agents, in the anaesthetized cat* A = *dose to produce* 50% *twitch block,* B = *Dose to reduce to* 50% *bradycardia produced by vagal stimulation*

Drug	Muscle	A (mg kg^{-1})	B (mg kg^{-1})	B/A	Reference
Org NC 45	Soleus	0.034	2.145	63.1	Durant and others (1979)
Tubocurarine	Soleus	0.2	0.25	1.2	Durant, Bowman and Marshall (1977)
	Gastrocnemius	0.13	0.18	1.4	Hughes and Chapple (1976)
Metocurine	Soleus	0.03	0.44	14.5	Durant and others (1977)
	Gastrocnemius	0.02	0.4	20.0	Hughes and Chapple (1976)
Pancuronium	Soleus	0.018	0.062	3.4	Durant and others (1979)
	Gastrocnemius	0.015	0.075	5	Hughes and Chapple (1976)
Alcuronium	Gastrocnemius	0.05	0.25	5	Hughes and Chapple (1976)
Fazadinium	Tibialis	0.8	0.45	0.6	Marshall (1973)
	Gastrocnemius	0.7	0.3	0.4	Hughes and Chapple (1976)
Gallamine	Gastrocnemius	1.0	0.6	0.6	Hughes and Chapple (1976)

bradycardial responses to stimulation of the right vagus. All the non-depolarizing agents in current use have been tested in this way and table V summarizes the relationship between neuromuscular and vagal blocking doses in the cat. It can be seen from table V that the drugs with low vagal/neuromuscular blocking ratios are the compounds associated with the production of tachycardia in man. Org NC 45 has an extremely high ratio and even doses of the drug many times greater than those required to produce neuromuscular block do not increase heart rate in experimental animals (Booij et al., 1980; Durant, Houwertjes and Crul, 1980). Figure 4 contrasts the effect of a neuromuscular blocking dose of gallamine in blocking the cardiac vagus with the absence of this effect of a neuromuscular blocking dose of Org NC 45.

Effects of Org NC 45 metabolites

As discussed by Savage, Sleigh and Carlyle (1980) in this supplement, it is probable that Org NC 45 is primarily metabolized to its 3-deacetyl derivative, Org 7268. Hydrolysis will also take place to form the 17-deacetyl derivative (Org NC 58) and finally to the 3,17-bis-deacetyl derivative (Org 7402).

In the isolated rat phrenic nerve–hemidiaphragm preparation the concentration of Org NC 45 producing 50% reduction of maximal responses to nerve stimulation is 3.4 µg ml^{-1}. The equiactive doses of the metabolites were: Org 7268 (3-OH) 5.16 µg ml^{-1}; Org NC 58 (17-OH) 34.2 µg ml^{-1}; Org 7402 (3,17-OH) 59.9 µg ml^{-1}.

TABLE VI. *Comparison of neuromuscular and vagal blocking activities in the anaesthetized cat of Org NC 45 and its metabolites.* (**From Durant et al.,* 1979). A = *Dose to produce* 50% *soleus twitch block;* B = *Dose to reduce to* 50% *bradycardia produced by vagal stimulation*

Compound	3- and 17-substituents	A (µg kg^{-1})	B (µg kg^{-1})	B/A
Org NC 45*	3,17-OAc	34	2145	63
Org 7268	3-OH,17-OAc	36	805	23
Org NC 58	3-OAc,17-OH	735	530	0.86
Org 7402	3,17-OH	1800	237	0.13

Thus, Org NC 45 is 1.5 times more potent than the 3-deacetyl metabolite, 10.1 times more potent than the 17-deacetyl derivative and 17.6 times more potent than the 3,17-bisdeacetyl derivative (L. H. D. J. Booij and F. van der Pol, unpublished observations).

The neuromuscular and vagal blocking activities of the three potential metabolites have also been compared in cats anaesthetized with chloralose (I. Marshall, unpublished observations). The results are summarized in table VI.

Thus Org NC 45 will probably hydrolyse to a compound which also possesses very low vagal blocking potency. Despite the 3,17-OH analogue possessing considerably greater vagal blocking potency than Org NC 45, it is unlikely that sufficient of the analogue will be formed from neuromuscular blocking doses of Org NC 45 to produce sufficient vagal block to lead to tachycardia.

Effects of pH on Org NC 45 neuromuscular block

The effects of acute changes in acid–base balance on the neuromuscular blocking action of Org

NC 45 have been studied in the pentobarbitone-anaesthetized cat and in the isolated phrenic nerve–hemidiaphragm preparation (Funk, Crul and van der Pol, 1980). In cats respiratory alkalosis (pH 7.53; Pa_{CO_2} 1.9 kPa) slightly but not significantly antagonized neuromuscular block produced by continuous infusion of Org NC 45 and slightly increased the cumulative dose required to produce 85–95% twitch blockade. Metabolic alkalosis (pH 7.64; Pa_{CO_2} 3.5 kPa) significantly antagonized neuromuscular block produced by infusion, but only slightly and not significantly increased the 85–95% blocking dose.

In contrast, respiratory acidosis (pH 6.98; Pa_{CO_2} 10.3 kPa) and metabolic acidosis (pH 7.13; Pa_{CO_2} 4.9 kPa) both significantly augmented block produced by an infusion of Org NC 45 and reduced the 85–95% blocking dose.

Similar results were obtained in the isolated rat hemidiaphragm in which alkaline conditions (pH 7.68) only slightly antagonized Org NC 45-induced neuromuscular block whereas acid conditions (pH 7.05) significantly augmented the block.

It is likely that these results may in part be attributed to an increased rate of metabolism of Org NC 45 by alkaline hydrolysis and a greater molecular stability during acidosis.

CONCLUSION

In animal experiments Org NC 45 has been shown to be a non-depolarizing neuromuscular blocking agent with a high potency, approximating to that of pancuronium. The onset and duration of action of Org NC 45 were found to be shorter than those of pancuronium. Repeated doses of Org NC 45 exhibited less cumulative effects than seen with tubocurarine or pancuronium. The neuromuscular block produced by Org NC 45 was antagonized by anticholinesterase agents and by aminopyridines. Also, its weak inhibitory actions against acetylcholinesterase and butyrylcholinesterase are unlikely to lead to poor antagonism by anticholinesterases or adverse interactions involving suxamethonium.

Org NC 45 has also been tested for effects at sites other than the skeletal muscle neuromuscular junction. The compound showed less propensity than other commonly used muscle relaxants to release histamine. Org NC 45 exhibited negligible ganglion blocking activity and a wide margin between neuromuscular and vagal blocking doses was seen. Although factors other than vagal block are likely to be involved in the tachycardia produced by many muscle relaxants, vagal block in the cat is a good indication that tachycardia is likely to occur in man. Thus it can be predicted from the above results that Org NC 45, at neuromuscular blocking doses, is unlikely to produce marked cardiovascular side-effects in man.

It can be predicted that Org NC 45 will hydrolyse fairly rapidly to its 3-deacetyl derivative which, like Org NC 45, possesses low vagal blocking activity. The proposed final metabolite, the 3,17-bis-deacetyl derivative, is unlikely to be produced in sufficient quantities to induce neuromuscular or vagal block.

Thus Org NC 45 is a highly potent compound with a high degree of selectivity for the receptors at the neuromuscular junction. It is probable that the compound will produce few cardiovascular side-effects in man and its emergence represents a potentially useful addition to the armamentarium of clinically useful muscle relaxants.

ACKNOWLEDGEMENTS

The authors would like to thank Professor W. C. Bowman for his assistance in the preparation of the manuscript. During the course of the work described, Dr N. N. Durant was supported by a Science Research Council C.A S.E. award. Test compounds were gifts from Organon Scientific Development Group, Newhouse

REFERENCES

Blogg, C. E., Savege, T. M., Simpson, J. C., Ross L. A., and Simpson, B. R. (1973). A new muscle relaxant-AH8165. *Proc. R. Soc. Med.*, **66**, 1023.

Booij, L. H. D. J., Edwards, R. P., Sohn, Y. J., and Miller, R. D. (1980). Cardiovascular and neuromuscular effects of Org NC 45, pancuronium, metocurine and d-tubocurarine in dogs. *Anesth. Analg.* (*Cleve.*), **59**, 26.

—— van der Pol, F., Crul, J. F. and Miller, R. D. (1980). Antagonism of Org NC 45 neuromuscular blockade by neostigmine, pyridostigmine and 4-aminopyridine. *Anesth. Analg.* (*Cleve.*), **59**, 31.

Bowman, W. C. (1980). *Pharmacology of Neuromuscular Function, with special Reference to Anaesthetic Practice.* Bristol: John Wright & Sons (in press).

Buckett, W. R., Hewett, C. L, and Savage, D. S. (1973). Pancuronium bromide and other steroidal neuromuscular blocking agents containing acetylcholine fragments. *J. Med. Chem.*, **16**, 1116.

—— Marjoribanks, C. E. B., Marwick, F. A., and Morton, M. B. (1968). The pharmacology of pancuronium bromide (Org NA 97), a new potent steroidal neuromuscular blocking agent. *Br. J. Pharmacol. Chemother.*, **32**, 671.

Durant, N. N., Bowman, W. C., and Marshall, I. G. (1977). A comparison of the neuromuscular and autonomic blocking activities of (+)-tubocurarine and its N-methyl and 0,0,N-trimethyl analogues. *Eur. J. Pharmacol.*, **46**, 297.

Durant, N. N., Houwertjes, M. C., and Crul, J. F. (1980). Comparison of the neuromuscular blocking properties of Org NC 45 and pancuronium in the rat, cat and rhesus monkey. *Br. J. Anaesth.*, **52**, 723.

—— Marshall, I. G., Savage, D. S., Nelson, D. N., Sleigh, T., and Carlyle, I. C. (1979). The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45 and other pancuronium analogues in the cat. *J. Pharm. Pharmacol.*, **31**, 831.

Funk, D. I., Crul, J. F., and van der Pol, F. M. (1980). Effects of changes in acid–base balance on neuromuscular blockade produced by Org NC 45. *Acta Anaesthesiol., Scand.*, **24**, 119.

Gandiha, A., Marshall, I. G., Paul, D., Rodger, I. W., Scott, W., and Singh, H. (1975). Some actions of chandonium iodide, a new short-acting muscle relaxant in anaesthetised cats and on isolated preparations. *Clin. Exp Pharmacol. Physiol.*, **2**, 159.

Hughes, R., and Chapple, D. J. (1976). Effects of non-depolarizing neuromuscular blocking agents on peripheral autonomic mechanisms in cats. *Br. J Anaesth.*, **48**, 59.

Kelman, G. R., and Kennedy, B. R. (1971). Cardiovascular effects of pancuronium in man. *Br. J. Anaesth.*, **43**, 335.

Kennedy, B. R., and Kelman, G R. (1970). Cardiovascular effects of alcuronium in man. *Br J. Anaesth.*, **42**, 625.

Krieg, N., Rutten, J., Crul, J. F. and Booij, L. H. D. J. (1980). Preliminary review of the interactions of Org NC 45 with anaesthetics and antibiotics in animals. *Br. J. Anaesth.* **52**, 33S.

McDowell, S. A., and Clarke, R S. J. (1969). A clinical comparison of pancuronium with d-tubocurarine. *Anaesthesia*, **24**, 581.

MacLagan, J. (1976). Competitive neuromuscular blocking drugs; in *Neuromuscular Junction Heffter's Handbook of Experimental Pharmacology* (ed. E. Zaimis), vol. 42, p. 421. Berlin: Springer-Verlag.

Marshall, I G. (1968). Studies on the neuromuscular blocking activity of some quaternary ammonium compounds. Ph.D. Thesis, University of Strathclyde

—— (1973). The ganglion blocking and vagolytic activities of three short-acting neuromuscular blocking agents in the cat. *J. Pharm. Pharmacol*, **25**, 530

Marshall, R. J., McGrath, J. C., Miller, R. D., Docherty, J., and Lamar, J.-C. (1980). Comparison of the cardiovascular actions of Org NC 45 with those produced by other non-depolarizing neuromuscular blocking agents in experimental animals. *Br. J. Anaesth.*, **52**, 21S.

Miller, R. D., Dennissen, P. A. F., van der Pol, F., Agoston, S., Booij, L. H. D. J., and Crul, J. F (1978). Potentiation of neostigmine and pyridostigmine by 4-aminopyridine in the rat. *J. Pharm Pharmacol.*, **30**, 699.

Riker, W. F., and Wescoe, W. C. (1951). The pharmacology of Flaxedil with observations on certain analogs. *Ann. N.Y. Acad Sci.*, **54**, 373.

Savage, D S., Sleigh, T., and Carlyle, I. C. (1980). The emergence of Org NC 45, 1-[(2β,3α,5α,16β,17β)-3,17-bis-(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methylpiperidinium bromide, from the pancuronium series. *Br. J. Anaesth.*, **52**, 3S.

Saxena, P. R., and Bonta, I L. (1970). Mechanism of selective cardiac vagolytic action of pancuronium bromide. Specific blockade of cardiac muscarinic receptors. *Eur. J Pharmacol.*, **11**, 332.

Smith, N. I, and Whitcher, C. E. (1967). Hemodynamic effects of gallamine and tubocurarine administered during halothane anesthesia. *J.A.M.A.*, **199**, 704.

Ungerer, M. J., and Erasmus, F. R. (1974). Clinical evaluation of a new non-depolarizing muscle relaxant. *S. Afr. Med. J*, **48**, 2561.

PHARMACOLOGIE D'ORG NC 45 COMPAREE A CELLES D'AUTRES AGENTS DE BLOCAGE NEUROMUSCULAIRE NON DEPOLARISANTS

RESUME

Parmi les résultats des tests pharmacologiques effectués sur le blocage autonome et neuromusculaire d'une série d'analogues du pancuronium, on a choisi Org NC 45, qui est l'analogue monoquaternaire C16 du pancuronium, pour faire l'objet d'une étude détaillée. Org NC 45 a un mécanisme d'action non dépolarisant, il a un début d'action plus rapide et une plus courte durée d'action que le pancuronium. Il entraîne moins d'accumulation que le pancuronium ou la tubocurarine et il est facile de le neutraliser à l'aide d'anticholinestérases et d'aminopyridines. Org NC 45 n'a qu'une faible tendance au dégagement d'histamine. Sa possibilité de freiner la cholinestérase ne semble pas avoir d'importance aux doses utilisées pour les blocages neuromusculaires. Org NC 45 a la possibilité de bloquer les ganglions, mais celle-ci est négligeable et il y a une grande marge entre les doses de blocage neuromusculaire et celles requises pour le blocage pneumogastrique. De ce fait, il est peu probable qu'il y ait des effets cardiovasculaires secondaires, lorsqu'on utilise Org NC 45. Il s'hydrolyse surtout avec son analogue 3-hydroxyle qui, comme Org NC 45, dispose d'une grande marge entre les doses requises pour le blocage neuromusculaire et celles nécessaires pour le blocage pneumogastrique. Org NC 45 a une haute sélectivité pour le carrefour neuromusculaire et constitue une addition potentiellement utile du point de vue clinique à l'arsenal des relaxants musculaires.

DIE PHARMAKOLOGIE VON ORG NC 45 IM VERGLEICH MIT ANDEREN NICHT-DEPOLARISIERENDEN NEUROMUSKULÄREN BLOCKIERUNGSDROGEN

ZUSAMMENFASSUNG

Aus pharmakologischen Testresultaten bezuglich der neuromuskularen und autonom blockierenden Wirkungen einer Reihe von Pancuronium-Derivaten wurde das C16 monoquaternare Derivat Org NC 45 fur detaillierte Untersuchungen ausgewählt. Org NC 45 hat einen nicht-depolarisierenden Aktionsmechanismus, die Wirkung tritt rascher ein und dauert kürzer als bei Pancuronium. Die Droge hat einen geringeren kumulativen Effekt als Pancuronium oder Tubocurarin, und ihre Wirkung kann leicht durch anticholinesterasen und Aminopyridine aufgehoben werden. Org NC 45 zeigt geringe Neigung zum Freimachen von Histaminen. Seine Eigenschaft, Cholinesterasen zu unterdrücken, dürfte bie den Dosen für neuromuskuläre Blockierung kaum von Bedeutung sein. Org NC 45 ist so gut wie nicht ganglienblockierend, und es besteht ein grosser Abstand zwischen der neuromuskularen und der vagalen Blockierung. Daher wird diese Droge kaum kardiovaskuläre Nebenerscheinungen hervorrufen. Es hydrolisiert hauptsächlich zu seinem 3-hydroxy-Derivat, das wie die Droge

selbst einen weiten Abstand zwischen neuromuskulärer und vagaler Blockierung zeigt. Org NC 45 zeigt eine hohe Selektivitat für neuromuskulare Verbindungsstellen und stellt eine wertvolle Ergänzung des Bestandes klinisch nützlicher Muskelentspannungsmittel dar.

LA FARMACOLOGIA DEL ORG NC 45 EN COMPARACION CON OTRAS DROGAS DE BLOQUEO NEUROMUSCULAR NO DESPOLARIZANTES

SUMARIO

Como consecuencia de los resultados de las pruebas farmacológicas sobre las acciones de bloqueo neuromuscular y autonómico de una serie de productos análogos al pancuronium, se seleccionó el Org NC 45, que es el producto monocuaternario C16 análogo al pancuronium, para llevar a cabo un estudio detallado. El Org NC 45 posee un mecanismo de acción no despolarizante, su acción es más rápida y el periodo de ésta es más corto que en el caso del pancuronium. Muestra menos acumulación que el pancuronium o que la tubocurarina, y se contrarresta fácilmente con anticolesterases y aminopiridinas. El Org NC 45 muestra una menor propensión a liberar histamina. Su habilidad para inhibir colinesterases no var a ser, seguramente, de importancia al nivel de dosis de bloqueo neuromuscular. El Org NC 45 posee una acción de bloqueo de los ganglios que es despreciable y existe un amplio margen entre las dosis de bloqueo neuromuscular y vagal. Es por esto que no es probable que se presenten efectos secundarios de tipo cardiovascular a causa del uso del Org NC 45. Se hidrolizará principalmente hasta su análogo 3-hidroxi el cual, al igual que el Org NC 45, posee un amplio margen entre las dosis de bloqueo neuromuscular y vagal. El Org NC 45 posee una alta selectividad para la confluencia neuromuscular y representa, a nivel potencial, una valiosa incorporación al arsenal de relajantes musculares de utilidad clínica.

UNIVERSITY COLLEGE OF MEDICINE LIBRARY

Br. J. Anaesth. (1980), 52, 21S

COMPARISON OF THE CARDIOVASCULAR ACTIONS OF ORG NC 45 WITH THOSE PRODUCED BY OTHER NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS IN EXPERIMENTAL ANIMALS

R. J. MARSHALL, J. C. MCGRATH, R. D. MILLER, J. R. DOCHERTY AND J.-C. LAMAR

SUMMARY

The cardiovascular actions of 1- [(2β,3α,16β,17β)-3,17-bis(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methyl-piperidinium bromide (Org NC 45) are reviewed and compared with those of other non-depolarizing neuromuscular blocking drugs. Results obtained in anaesthetized cats and dogs have demonstrated that, in contrast to other neuromuscular blocking drugs, Org NC 45, even in doses 20 times greater than those required for neuromuscular block, has no effects on heart rate, arterial pressure, autonomic ganglia, adrenoceptors or baroreceptor activity. Studies in pithed rats and on guineapig atria have further shown that Org NC 45 has little effect on cardiac muscarinic receptors or on noradrenaline re-uptake mechanisms. These results suggest that Org NC 45 possesses significant advantages over presently used non-depolarizing neuromuscular blocking drugs, since its clinical use should not be associated with cardiovascular side-effects.

Since the introduction of tubocurarine into the clinical practice of anaesthesia, medicinal chemists have striven to design compounds which possess fewer side-effects. The main disadvantages of tubocurarine are first its relatively long duration of action and second its ability to cause marked hypotension (Thomas, 1957), an effect thought to be the result of blockade of autonomic ganglia (Guyton and Reeder, 1950; Randall, 1951), the release of histamine (Comroe and Dripps, 1946; MacIntosh and Paton, 1949) and possibly also a direct depressant effect on the heart (Johnston, Mahmoud and Mrozinski, 1978). Whilst only moderate success has been achieved in producing shorter-acting non-depolarizing neuromuscular blocking drugs, a clear separation between neuromuscular and ganglion blocking properties has been obtained with gallamine, pancuronium, alcuronium and the experimental azasteroid, chandonium (Buckett et al., 1968; Hughes and Chapple, 1976; Gandiha et al., 1975). Furthermore, pancuronium and fazadinium, even in high concentrations, do not cause release of histamine in anaesthetized animals (Buckett and Frisk-Holmberg, 1970; Brittain and Tyers, 1973; MacLagan, 1976; Ertama, 1978).

However, it is clear that neuromuscular blocking doses of gallamine, pancuronium, alcuronium and fazadinium can cause tachycardia in man (Smith and Whitcher, 1967; Kennedy and Kelman, 1970; Kelman and Kennedy, 1971; Blogg et al., 1973; Savege et al., 1973). Although these increases in heart rate have usually been attributed to post-ganglionic vagal block (blockade of cardiac muscarinic receptors), a sympathetic component has been postulated both for gallamine (Brown and Crout, 1970), and more recently for pancuronium (Nana, Cardan and Domokos, 1973; Ivankovich et al., 1975; Domenech et al., 1976).

These observations have prompted more detailed studies of the mechanisms underlying the cardiovascular actions of neuromuscular blocking drugs and much of this work has been recently discussed in an excellent review (Marshall, 1980). The purpose of this paper is to describe studies on the cardiovascular actions of the newly developed neuromuscular blocking drug, Org NC 45, an analogue of pancuronium (Durant et al., 1979), and to compare these actions with those of other agents used clinically.

R. J. MARSHALL,* B.SC., PH.D., Department of Physiology and Pharmacology, University of Strathclyde, Glasgow. J. C. MCGRATH, B.SC., PH.D.; J. R. DOCHERTY, B.SC., PH.D.; Department of Physiology, University of Glasgow, Glasgow. R. D. MILLER, M.D., Department of Anesthesia and Pharmacology, University of California, San Francisco, U.S.A. J.-C. LAMAR, Scientific Development Group, Organon International B.V., Oss, Holland.

* Present address, for reprints: Scientific Development Group, Organon Laboratories Limited, Newhouse, Lanarkshire ML1 5SH.

0007-0912/80/130021-12 $01.00

© Macmillan Publishers Ltd 1980

(P25769

METHODS

Haemodynamic studies in anaesthetized cats

Cats of either sex were anaesthetized either with 2.2 ml kg^{-1} of an i.v. mixture of 25% urethane, 2% chloralose and 1% borax or with sodium pentobarbitone 30 mg kg^{-1} (acute lethal studies). They were artificially ventilated with room air by means of a Palmer pump, at a frequency of 20 b.p.m. and a tidal volume producing an arterial $P\text{CO}_2$ of 3.7–4.3 kPa. Arterial pressure was measured by a femoral artery cannula connected to a P23Ac Statham transducer. Heart rate was triggered from the electrocardiogram and recorded by means of an instantaneous beat-to-beat recording tachography preamplifier (7P4D Grass). In the cats anaesthetized with the urethane–chloralose mixture, the effects of Org NC 45 on the responses to bilateral carotid artery occlusion (for 30 s), on responses to pre- and post-ganglion stimulation of the nictitating membranes (50 Hz, 1 ms for 10 s), and on the changes in arterial pressure and heart rate elicited by i.v. injection of either noradrenaline <5 μg kg^{-1} or isoprenaline <5 μg kg^{-1} were studied. After at least two control runs, increasing doses of Org NC 45 (0.01, 0.10 and 1.0 mg kg^{-1}) were administered i.v. at intervals of 1 h. Two runs were carried out after each dose of Org NC 45 and the results were measured and compared with those obtained in a group of untreated cats.

In the animals anaesthetized with pentobarbitone, the effects of six doses of Org NC 45 (0.1–30 mg kg^{-1}) on arterial pressure, heart rate and the e.c.g. were investigated ($n = 9$) and compared with effects of corresponding volumes of the buffered vehicle (citric acid, disodium phosphate and mannitol; $n = 3$). Consecutive doses of Org NC 45 (or vehicle) were administered i.v. at 30-min intervals.

Haemodynamic studies in anaesthetized dogs

Eight beagle dogs of either sex and weighing 9–12 kg were anaesthetized with sodium pentobarbitone 30 mg kg^{-1} i.v. They were intubated and respired with room air by means of a Pneumador ventilator at a frequency of 20 b.p.m. and an inspiration/expiration ratio producing an arterial $P\text{CO}_2$ of 3.7–4.3 kPa. If necessary the level of anaesthesia was maintained with 60-mg bolus injections of sodium pentobarbitone. Arterial $P\text{O}_2$, $P\text{CO}_2$ and pH were measured throughout each experiment (using a Corning 175 automatic blood-gas analyser) and were corrected for rectal temperature of the animal. Arterial pressure was measured from a catheter passed into the aortic arch via a carotid artery, and left ventricular pressure was recorded from a Millar micro-tip transducer introduced via the left cranial thyroid artery. Left ventricular dP/dt was obtained from left ventricular pressure using a Grass differentiator (7P20B).

After a 30-min control period, six dogs received increasing doses of Org NC 45 (0.1–30 mg kg^{-1}) i.v. while the remaining two animals received corresponding volumes of vehicle. Injections were given every 30 min.

Studies in pithed rats

Male Wistar rats (250–300 g) were pithed by the method of Gillespie, MacLaren and Pollock (1970) and ventilated with 100% oxygen at a rate of 60 b.p.m. and using a stroke volume of 1 ml per 100 g (Clanachan and McGrath, 1976). Arterial pressure was recorded from a catheter in a carotid artery and this signal used to trigger a Devices instantaneous heart rate meter.

The spinal outflows at C6-T1 were stimulated electrically through the pithing rod with short single pulses (0.05 ms) of supramaximal voltage in order to stimulate the sympathetic outflow to the heart selectively and to produce contraction of forelimb skeletal muscles. In separate experiments the peripheral portion of the divided right cervical vagus was stimulated at 2-min intervals for 10 s (5 Hz, 1 ms, supramaximal voltage). Drugs other than Org NC 45 were dissolved in 0.9% w/v sodium chloride solution. Org NC 45 was dissolved in acetate buffer. All drugs were injected i.v. in a volume of 1 ml kg^{-1} and washed in with saline 1 ml kg^{-1}. For control purposes, injections of saline 2 ml kg^{-1} or a corresponding volume of Org NC 45 vehicle (acetate buffer) were also administered.

Studies on isolated guineapig atria

Guineapigs (Dunkin–Hartley) weighing 200–320 g were killed by stunning and exsanguination and either the paired atria or the left atrium were quickly excised and placed in a 10-ml organ bath containing Krebs–Henseleit salt solution of composition (g litre^{-1}): NaCl 6.9, KCl 0.35, $NaHCO_3$ 2.1, KH_2PO_4 0.16, $MgSO_4$ 0.29, $CaCl_2$ 0.56, glucose 2.0, bubbled with carbogen and maintained at 32 °C (left atria) or 37 °C (paired preparations). The left atrial preparations were stimulated through a platinum electrode with supra-threshold (3–7 V) square wave pulses of 5 ms duration at a frequency of 2 Hz. Contractions of atrial preparations were measured by attaching the free end of the atria by means of a thin cotton thread to a strain gauge transducer (Ether UFI) and were recorded on a two-channel recorder (Devices M2). Initial resting tensions of 1.0 and 0.5 g were applied to paired and left atrial preparations respectively. Spontaneously beating paired atrial preparations were used to study only chronotropic effects, the rate of beating being measured as the number of contractions occurring in 12 s and expressed as beat min^{-1}. For assessment of muscarinic receptor antagonism, cumulative concentration–response curves were obtained for acetylcholine 0.6–16.5 $\times 10^{-7}$ mol litre^{-1} or pilocarpine 0.4–14.8 $\times 10^{-6}$ mol litre^{-1} in tissues taken from reserpinized animals (5 mg kg^{-1} i.p. 24 h previously).

After a reproducible concentration–response relationship to an agonist was obtained, additions of the agonist were repeated, 20 min after the administration of a neuromuscular blocking drug to the organ bath. At least three concentrations of neuromuscular blocking drug were used in each preparation. Org NC 45 was used as the water-soluble hydrochloride. Responses were expressed as a percentage decrease in developed tension (or rate of beating) and dose ratios (between the last control curve and the curve obtained in the presence of test drug) were calculated at the 50% level. Calculations of pA_2 values for antagonism of the negative chronotropic or inotropic responses to agonists were carried out by the method of Arunlakshana and Schild (1959).

In order to assess effects on the cardiac sympathetic neuro–effector junction, the ability of the neuromuscular blocking drugs to modify the positive inotropic actions of (−)-noradrenaline and (−)-isoprenaline were investigated in driven left atria incubated in Krebs–Henseleit solution containing atropine 1.4×10^{-6} mol litre^{-1}. Cumulative concentration–response curves to either (−)-noradrenaline or (−)-isoprenaline were repeated until consistent responses were obtained. The same procedure was repeated after 30 min of incubation with one concentration of neuromuscular blocking drug. Any shift in the concentration–response curve was noted and expressed as a dose ratio at the 50% maximum level. No change in sensitivity to the agonist was found in untreated preparations, so that no correction for sensitivity change with time was necessary.

Studies in isolated guineapig ileum

Segments of ileum 1–2 cm in length were taken from reserpinized animals and suspended under a resting tension of approximately 0.5 g in oxygenated Krebs–Henseleit solution at 32 °C and containing propranolol 10^{-7} mol litre^{-1} and hexamethonium 2×10^{-6} mol litre^{-1}. Single concentrations of acetylcholine were added every 5 min and left in contact with the tissue for 25 s. After consistent concentration–response curves were obtained (usually three), they were repeated after 20 min of incubation with a concentration of atropine or neuromuscular blocking drug. At least three concentrations of antagonist were used in each preparation. pA_2 values were calculated as for guineapig atria.

RESULTS

Haemodynamic effects of Org NC 45 in anaesthetized cats

In chloralose–urethane anaesthetized cats, i.v. bolus injections of Org NC 45 0.01–1.0 mg kg^{-1} caused no changes in arterial pressure or heart rate and, in addition, did not modify the cardiovascular changes produced by either bilateral carotid occlusion or injection of noradrenaline or isoprenaline (fig. 1). Responses of the nictitating membrane to either pre- or post-ganglionic stimulation of the cervical sympathetic nerves were also unaffected by these doses of Org NC 45 and the drug was without effect on the resting tension of this organ.

A similar lack of haemodynamic effects of these doses of Org NC 45 was found in animals anaesthetized with pentobarbitone. However, greater i.v. doses (3.0–30 mg kg^{-1}) did cause dose-dependent but transient decreases in arterial pressure, of from 2.4 to 12.4 kPa, which were accompanied by equally transient periods of bradycardia of between 20 and 58 beat min^{-1}.

Haemodynamic effects of Org NC 45 in anaesthetized dogs

The effects of Org NC 45 0.1–30 mg kg^{-1} on heart rate and arterial pressure are summarized in figure 2. Doses of 0.1, 0.3 and 1.0 mg kg^{-1} of Org NC 45 produced transient and small decreases in arterial pressure ($<$ 0.4 kPa) which were accompanied by a slight tachycardia (range

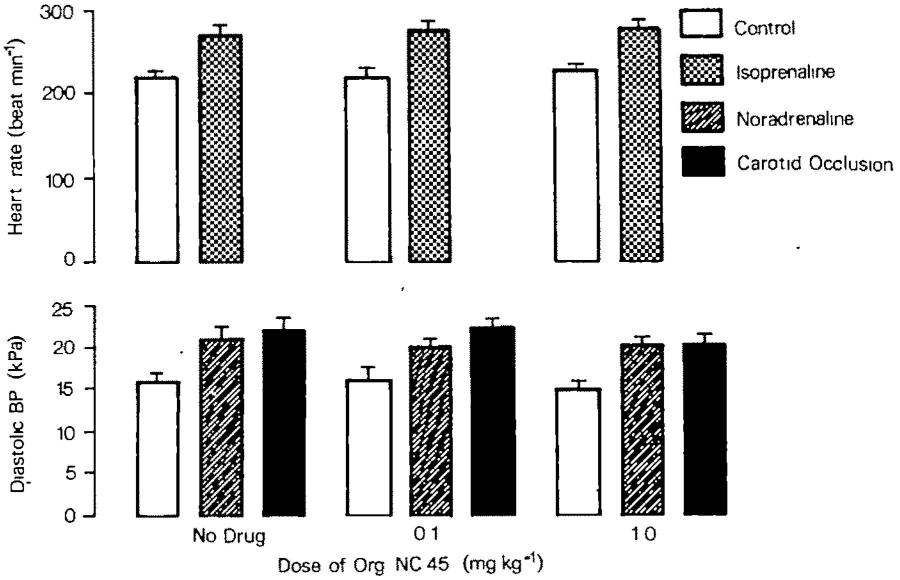


FIG 1. Effects of Org NC 45 on heart rate and diastolic arterial pressure (BP) and on the changes produced by isoprenaline, noradrenaline and carotid occlusion in chloralose–urethane anaesthetized cats ($n = 6$).

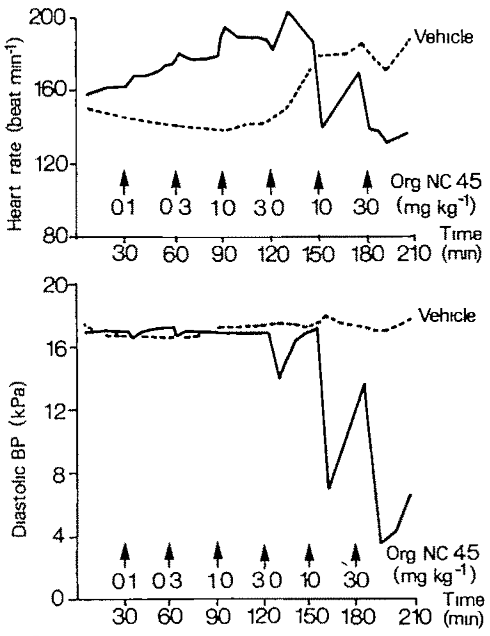


FIG. 2 Comparison of the effects on heart rate and diastolic arterial pressure (BP) of increasing doses of Org NC 45 with those of corresponding volumes of drug vehicle in sodium pentobarbitone-anaesthetized dogs.

6–20 beat min^{-1}) and small increases in left ventricular dP/dt max (between 2 and 8%). Larger doses of Org NC 45 (3.0, 10 and 30 mg kg^{-1}) caused marked dose-dependent decreases in arterial pressure and bradycardia, which were accompanied by brief (1–10 min) periods of hypercapnia (as assessed from expired carbon dioxide monitored with a capnograph). Even at these large doses Org NC 45 did not cause any abnormalities in the e.c.g. or in arterial blood-gases.

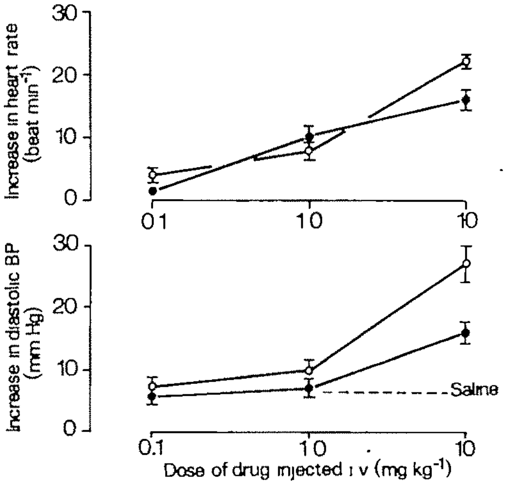


FIG. 3. Comparison of the effects of pancuronium (○) and Org NC 45 (●) on heart rate and diastolic arterial pressure (BP) in pithed rats Each point is the mean of at least five determinations.

Comparison of the autonomic effects of Org NC 45 and pancuronium in pithed rats

Following i.v. injection, pancuronium bromide 0.1–10 mg kg^{-1} produced dose-related increases in heart rate and arterial pressure which reached a maximum in 0.5–5 min, and declined to baseline within 2–10 min (fig. 3). Org NC 45 in doses of 1.0 and 10 mg kg^{-1} also produced transient tachycardia and increases in arterial pressure which waned over 6–10 min (fig. 3). The cardiac responses (but not the vasopressor actions) of pancuronium were abolished by pretreatment with propranolol 0.2 mg kg^{-1} and they were reduced by chemical sympathectomy with 6-hydroxydopamine. Both pancuronium 0.1–20 mg kg^{-1} and Org NC 45 1.0–10 mg kg^{-1} potentiated, in a dose-related manner, the cardioaccelerator response to single pulse stimulation, although the effects of Org NC 45 were of short duration (<5 min) and lesser magnitude. The effects of pancuronium and Org NC 45 are summarized in figure 4 and are compared with those produced by cocaine and gallamine. Clearly cocaine 0.5 mg kg^{-1} produced effects similar in magnitude to those of the greater doses of pancuronium whereas gallamine 10 mg kg^{-1} produced no effect.

The duration of the potentiation produced by both pancuronium and Org NC 45 was dose-dependent and varied from 1 to >15 min for pancuronium and from 1 to 3 min for Org NC 45. Equivalent doses (those producing a similar

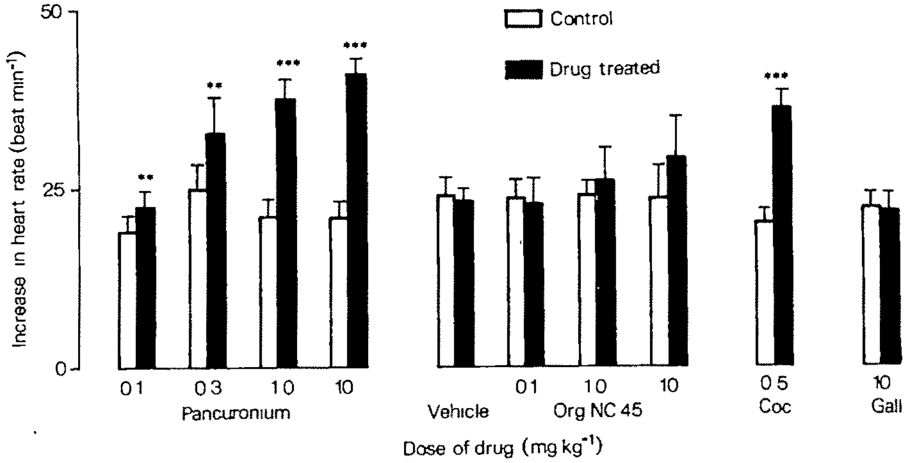


FIG. 4. Comparison of the effects of pancuronium, Org NC 45, the vehicle of Org NC 45, cocaine (Coc.) and gallamine (Gall.) on the cardioaccelerator response to single stimulus pulses. Open columns = control; black columns = 5 min after test drug. $^{**}P<0.01$; $^{***}P<0.001$)

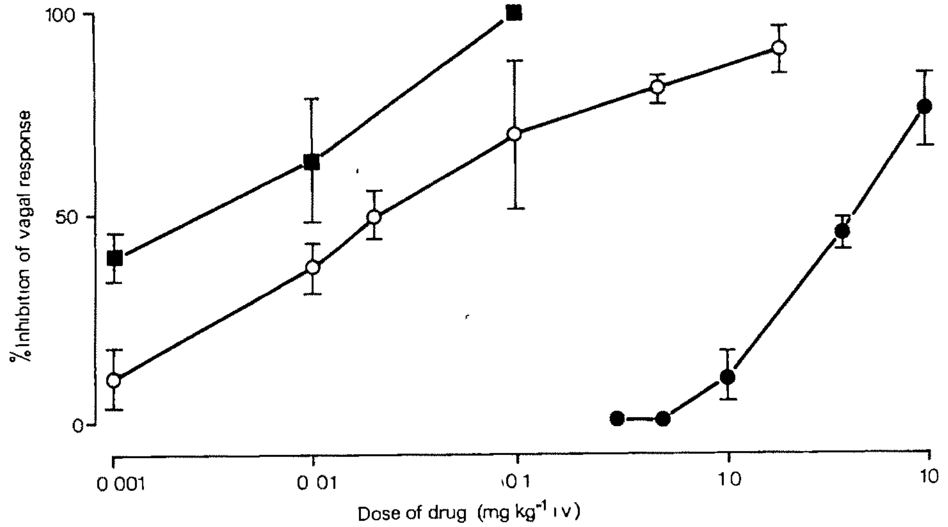


FIG. 5 The inhibition caused by atropine (■), pancuronium (○) and Org NC 45 (●) of the bradycardia induced by vagal stimulation in the pithed rat.

potentiation over a similar time) of pancuronium and Org NC 45 were 0.3 mg kg^{-1} and 10 mg kg^{-1} respectively.

The dose-response curves for the inhibition of the bradycardia produced by stimulation of the vagus are shown in figure 5, which demonstrates the shallowness of the curves produced by pancuronium, Org NC 45 and the standard muscarinic antagonist, atropine. The doses producing 50% inhibition of the response to vagal stimulation were atropine 0.003 mg kg^{-1}, pancuronium 0.008 mg kg^{-1} and Org NC 45 4.3 mg kg^{-1}.

Comparison of the effects of Org NC 45 with those of pancuronium, (+)-tubocurarine, fazadinium and chandonium in isolated guineapig atria

In isolated, electrically driven left atrial preparations taken from reserpinized guineapigs, all of the neuromuscular blocking drugs studied antagonized the negative inotropic actions of pilocarpine and acetylcholine. The results are summarized in table I. Analysis of the Schild plots, and the ease with which the effects could be abolished by washing, suggested that the antagonism was competitive except in the case of (+)-tubocurarine.

TABLE I. *Muscarinic receptor antagonist potencies of a series of non-depolarizing neuromuscular blocking agents in guineapig electrically driven left atria. Values are means ± SEM of least four determinations*

	v Acetylcholine		*v*. Pilocarpine	
Antagonist	pA_2	Slope	pA_2	Slope
(+)-Tubocurarine	—	—	5.2±0.6	0.6±0.4
Pancuronium	7.0±0.1	0.8±0.1	7.0±0.2	0.7±0.2
Fazadinium	6.5±0.1	0.6±0.2	6.3±0.1	0.7±0.1
Chandonium	7.4±0.2	1.2±0.3	7.4±0.3	1.0±0.3
Org NC 45	4.6±0.1	0.8±0.1	4.9±0.3	0.9±0.2

TABLE II. *The maximum potentiation produced by a series of non-depolarizing neuromuscular blocking agents of the positive inotropic actions of (−)-noradrenaline in guineapig electrically driven left atria*

Drug	Concentration (μmol litre^{-1})	Maximum mean dose ratio	*n*
Pancuronium	7.0	10.4±2.1	5
Chandonium	16.0	7.7±2.0	9
Fazadinium	33.0	6.6±0.4	5
(+)-Tubocurarine	29.0	0.7±0.2	4
Org NC 45	29.0	1.8±0.4	6
Cocaine	8.8	11.6±0.3	6

Under the same experimental conditions (32 °C, 20 min contact time) atropine had a pA_2 8.8±0.1 ($n = 5$). Essentially similar results were obtained against the negative chronotropic actions of pilocarpine on paired atria (37 °C), the pA_2 values being pancuronium 6.6±0.1 (slope 0.9±0.4), Org NC 45 5.4±0.5 (slope 0.8±0.4) and atropine 8.7±0.2 (slope 0.8±0.1).

In order to assess effects on the cardiac sympathetic neuro-effector junction, the abilities of the neuromuscular blocking drugs and of the standard neuronal uptake blocking drug, cocaine, to modify the positive inotropic actions of (−)-noradrenaline and (−)-isoprenaline were investigated in electrically driven guineapig left atria incubated with atropine 1.4 μmol litre^{-1}. This concentration of atropine did not itself affect the dose-response curves to the amines. Cocaine 8.8 μmol litre^{-1} significantly potentiated the effects of (−)-noradrenaline (eight to 12-fold shift to the left) but left responses to (−)-isoprenaline unaffected (dose ratio of 0.96±0.14). Similar effects were observed with pancuronium 0.7–28 μmol litre^{-1}, fazadinium 8–33 μmol litre^{-1} and the experimental azasteroid, chandonium 8–33 μmol litre^{-1}. In contrast, even high concentrations of (+)-tubocurarine (29 μmol litre^{-1}) and Org NC 45 (29 μmol litre^{-1}) did not affect responses to either catecholamine. The maximum shifts in the noradrenaline concentration-response curves are shown in table II, and the selectivity of the effects of pancuronium are shown in figure 6.

In tissues incubated with cocaine 8.8 μmol litre^{-1} for 1 h, pancuronium 14 μmol litre^{-1} did not potentiate the effects of (−)-noradrenaline, the ED_{50} values for the catecholamine being 4.8±0.6 × 10^{-9}mol litre^{-1} before and 5.5±0.8 × 10^{-9}mol litre^{-1} 30 min after pancuronium ($P > 0.05$).

In concentrations which caused potentiation of the cardiac actions of noradrenaline, pancuronium itself (2.8–14 μmol litre^{-1}) caused concentration-dependent increases in developed tension which, however, never exceeded 28% of the maximum response to isoprenaline or noradrenaline. This positive inotropic action of these concentrations of pancuronium would seem to be mainly a result of release of noradrenaline, since it was almost abolished by propranolol 1.7 μmol litre^{-1} and greatly reduced after treatment with cocaine 8.8 μmol litre^{-1} (fig. 7). In contrast, Org NC 45 caused only transient positive inotropic effects (13–17% isoprenaline maximum) at very great concentrations (15–75 μmol litre^{-1}) and these effects were unaffected by propranolol.

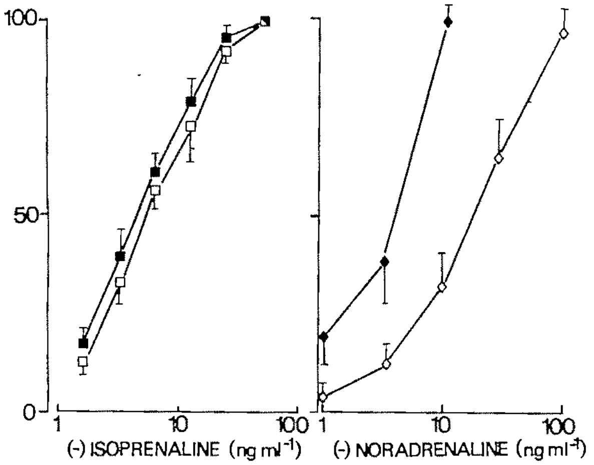


FIG. 6. Effects of pancuronium 5.0 μg ml^{-1} (■) and 2.0 μg ml^{-1} (◆) on the positive inotropic responses (% maximum increase in developed tension) to (−)noradrenaline (◇) and (−)isoprenaline (□) in guineapig electrically driven left atria.

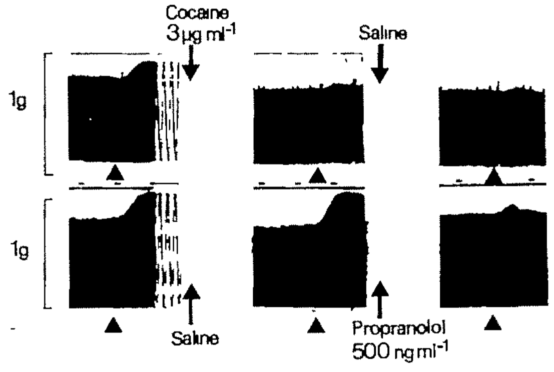


FIG. 7. The effects of cocaine and propranolol on the positive inotropic effects of pancuronium in guineapig electrically driven left atria. ▲ = pancuronium 10 μg ml^{-1}

The effects of Org NC 45, pancuronium and atropine on ACh-induced contractions of guineapig ileum

In segments of ileum taken from reserpinized guineapigs, both atropine and pancuronium produced concentration-dependent and parallel shifts to the right of acetylcholine concentration–response curves. The calculated pA_2 values were: atropine 8.6±0.2 (slope 1.02±0.08); pancuronium 4.5±0.4 (slope 0.62±0.18). In concentrations up to its limits of solubility ($\sim 10^{-2}$ mol litre^{-1}), Org NC 45 caused a maximum two to five-fold shift to the right of the acetylcholine dose–response curves which was associated with a depression of the maximal ACh response. Consequently, no pA_2 value could be calculated for Org NC 45.

DISCUSSION

Results obtained in ventilated pentobarbitone-anaesthetized cats and dogs, have clearly demonstrated that Org NC 45, in doses (1 mg kg^{-1}) approximately 20 times greater than those producing neuromuscular blockade (Durant, 1978), is devoid of marked effects on either arterial pressure or heart rate. In addition, in cats anaesthetized with α-chloralose and urethane, similar doses of Org NC 45 were shown to have no significant effects on either sympathetic autonomic ganglia, on α- and β-adrenoceptors or on baroreceptor reflex activity. Haemodynamic effects were seen only with doses greater than 3 mg kg^{-1} in both species studied and comprised dose-dependent decreases in arterial pressure and heart rate accompanied by slight hypercapnia. Even at very large doses of Org NC 45 (30 mg kg^{-1}), no abnormalities in the e.c.g. were observed. Of more direct relevance to the anaesthetist are the recent observations by Booij and others (1980) who compared the cardiovascular effects of comparable neuromuscular blocking doses (3 × ED_{90}) of Org NC 45 with those of pancuronium, metocurine and (+)-tubocurarine in halothane-anaesthetized dogs. In their study, pancuronium, metocurine and (+)-tubocurarine all caused significant increases in heart rate. Pancuronium also increased mean arterial pressure and cardiac output, whereas tubocurarine significantly decreased these parameters. In contrast, Org NC 45 produced no significant changes in any cardiovascular parameter measured.

It has also been demonstrated in monkeys anaesthetized with ketamine and pentobarbitone, that Org NC 45 does not cause tachycardia, whereas a comparable neuromuscular blocking dose of pancuronium (10 × ED_{50}) produces a small increase in heart rate of 10–15 beat min (Durant, 1978). Experiments in pithed rats (described in this paper and more fully elsewhere: Docherty and McGrath, 1978, 1980) and in isolated guineapig atria have also shown that Org NC 45 is some 15–20 times less active than pancuronium in stimulating the heart.

Experimental studies both *in vivo* and *in vitro* have shown that the tachycardia produced by most neuromuscular blocking drugs in man may involve more than one mechanism, and it may be pertinent to review these here briefly, especially in relation to the pharmacological profile of Org NC 45.

Ganglion blockade

There is good evidence in anaesthetized cats that (+)-tubocurarine and fazadinium block vagal transmission and autonomic ganglia in the dose ranges required to produce neuromuscular blockade (Marshall, 1973; Hughes and Chapple, 1976; Durant, Bowman and Marshall, 1977). Thus, at least a component of the tachycardia produced by these neuromuscular blocking drugs both in animals (Brittain and Tyers, 1973; Booij et al., 1979) and in man (Coleman et al., 1972; Stoelting, 1972) may be the result of blockade of parasympathetic ganglia (resulting in vagal inhibition).

In the present studies no evidence of ganglion blockade was found with Org NC 45 in concentrations (1 mg kg^{-1}) some 10 times greater than those required for block of neuromuscular transmission; this confirms the findings of Durant and others (1979) (see also Marshall et al., 1980—this symposium).

Blockade of postjunctional muscarinic receptors

In 1951, Riker and Wescoe observed that gallamine blocked cardiac muscarinic receptors. More recently, an atropine-like action has been demonstrated for pancuronium (Saxena and Bonta, 1970), alcuronium (Hughes and Chapple, 1976), fazadinium (Marshall, 1973) and the experimental azasteroid, chandonium (Gandiha et al., 1975). The present studies have demonstrated that Org NC 45 is some 500 times less potent than pancuronium in blocking the bradycardia produced by vagal stimulation in pithed rats, and in guineapig paired atria it has only 1/25 the affinity of pancuronium for cardiac muscarinic receptors subserving chronotropic responses. These results confirm the earlier findings of Durant and colleagues (1979) who showed, in anaesthetized cats, that although approximately equipotent with pancuronium in blocking neuromuscular transmission, Org NC 45 was some 35 times less active in blocking cardiac responses to vagal stimulation.

Previous studies have suggested that the muscarinic antagonist properties of neuromuscular blocking drugs seem to be confined to the muscarinic receptors in the heart, since those in the gut and on vascular smooth muscle are only blocked by greater concentrations of the drugs (Bonta, Goorissen and Derkx, 1968; Marshall, 1973; Hughes and Chapple, 1976), whereas atropine has similar affinity for muscarinic receptors no matter where they are situated (Rathbun and Hamilton, 1970; Saxena and Bonta, 1970; Marshall and Ojewole, 1979). It was of interest to note in the present studies that this selectivity of muscarinic receptor blockade also held true for Org NC 45 in guineapig cardiac and intestinal tissue. Whether these results provide evidence for the existence of two distinct populations of muscarinic receptors is not entirely clear at the moment, since it has been postulated that the effects of neuromuscular blocking drugs on cardiac muscarinic receptors may be more complicated than can be wholly explained by a classical competitive postsynaptic action (Clark and Mitchelson, 1976; Li and Mitchelson, 1978; Waud, Lee Son and Waud, 1978). This topic is more fully discussed by Marshall (1980).

Blockade of prejunctional muscarinic receptors

Constriction of certain isolated blood vessels such as the rabbit ear artery (Steinsland, Furchgott and Kirkepar, 1973; Rand and Varma, 1970; Hume, De la Lande and Waterson, 1972) and dog saphenous vein (Vanhoutte, 1977) evoked by sympathetic nerve stimulation is inhibited by muscarinic agonists. This inhibitory effect (which is blocked by atropine) is caused by a reduction in the release of sympathetic transmitter as a result of stimulation of the pre-junctional muscarinic receptors situated on the sympathetic nerve terminals. These prejunctional muscarinic receptors would seem to resemble the postsynaptic receptors in the heart, since they are readily blocked by micromolar concentrations of gallamine and pancuronium (Vercruysse et al., 1979). Recently Bowman and Houston (personal communication) have confirmed this prejunctional muscarinic antagonist action of pancuronium in isolated rabbit ear artery and have shown that Org NC 45 (up to 29 μmol $litre^{-1}$) does not antagonize these prejunctional receptors (fig. 8). If, in the heart, the

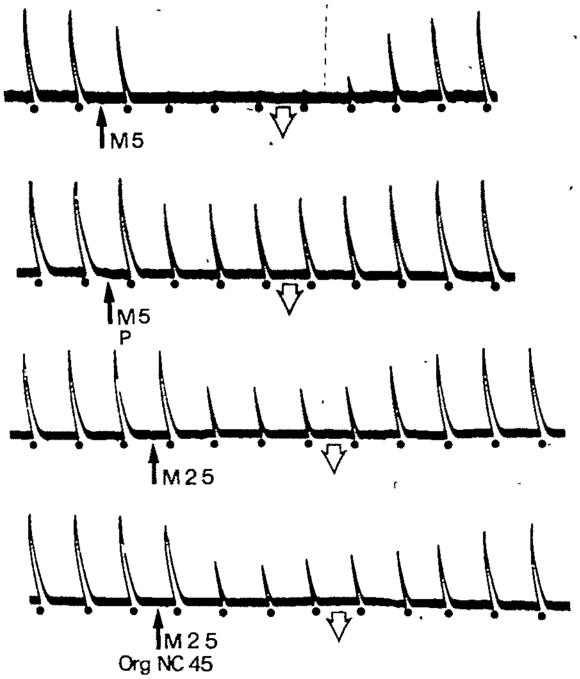


FIG. 8. Comparison of the effects of pancuronium 5 µg ml^{-1} (P) and Org NC 45 20 µg ml^{-1} on the metacholine-induced (M) inhibition of vasoconstrictor responses induced by sympathetic nerve stimulation (●) of rabbit ear arteries pretreated with cocaine 3 µg ml^{-1} in order to block noradrenaline re-uptake. (M 5 = metacholine 5 µg ml^{-1}, M 2.5 = metacholine 2.5 µg ml^{-1}.) In the test situation either pancuronium or Org NC 45 was administered just before the addition of metacholine (at black arrow) and the tissues were washed by overflow at the white arrow.

neural release of noradrenaline is partly controlled by parasympathetic nerves forming synapses on the sympathetic nerve terminals (for review see Shepherd et al., 1978) it is tempting to speculate that blockade of presynaptic muscarinic receptors produced by neuromuscular blocking drugs may also play a role in the production of tachycardia (Bowman, 1980). The weak muscarinic antagonist properties of Org NC 45 would suggest that this mechanism would not be relevant with clinical concentrations of this drug.

Noradrenaline release and re-uptake

Evidence is accumulating that the tachycardia produced by some neuromuscular blocking agents may have a sympathetic component. Thus, pancuronium has been shown to increase plasma catecholamine concentrations (Nana, Cardan and Domokos, 1973), both pancuronium and gallamine have been shown to have indirect sympathomimetic effects (Brown and Crout, 1970; Domenech et al., 1976), and pancuronium has been shown to inhibit the neuronal re-uptake of noradrenaline (Ivankovich et al., 1975; Docherty and McGrath, 1978; Tomlinson, 1979; Salt, Barnes and Conway, 1980). The present studies extend these findings to include fazadinium and chandonium, both of which potentiated the effects of (−)-noradrenaline (but not of isoprenaline) in guineapig atria.

Org NC 45 was approximately 30 times less active than pancuronium in potentiating the effects of sympathetic cardio-accelerator stimulation in pithed rats and did not potentiate the cardiac effects of noradrenaline in guineapig atria. It has also been shown *in vitro* and *in vivo* that the contractile response of rat vas deferens to adrenergic nerve stimulation is also potentiated to a relatively greater degree by pancuronium than by Org NC 45. This indicates that the potentiating effects are not confined to the sympathetic nerves in the heart and that the relative potencies of the two drugs are similar in different organ systems (Docherty and McGrath, 1980). Confirmation of these observations has been recently provided by Salt, Barnes and Conway (1980) who have shown that Org NC 45 is four times less potent than pancuronium in inhibiting the neuronal uptake of tritiated noradrenaline into perfused rat hearts. In perfused rabbit ear artery preparations, Bowman and Houston (personal communication) have shown that pancuronium, but not Org NC 45, can potentiate the sympathetic vasoconstrictor responses induced by electrical stimulation.

It is clear that the cardiovascular side-effects produced by different competitive neuromuscular blocking drugs involve one or more of several mechanisms. In anaesthetic practice, the importance of each component will also depend largely on the patient's autonomic balance which itself will be determined by the patient's medical history, the choice of premedicants given, the particular anaesthetic used and any concomitant therapy such as tricyclic anti-depressants, anti-hypertensives or α- or β-adrenoceptor antagonists. What seems clear is that Org NC 45 would seem to offer a major advance in the search for an "ideal" non-depolarizing neuromuscular blocking agent in that, although its potency and duration of action at the neuromuscular junction are similar to those of pancuronium and fazadinium, its clinical use could be expected to be associated with little or no effects on the cardiovascular system.

ACKNOWLEDGEMENTS

We should like to thank Ms A. H. B. Jones for typing the manuscript and Ian Ramsden, A.I.I.P., A.I.M.B.I., for preparing the illustrations. We also acknowledge the help of Professor W C. Bowman for constructive criticism of the manuscript and for allowing us to use unpublished data (figure 8).

REFERENCES

Arunlakshana, O., and Schild, H. O. (1959). Some quantitative uses of drug antagonists. *Br. J. Pharmacol. Chemother.*, **14**, 48.

Blogg, C E., Savage, T. M., Simpson, J. C., Ross, L. A., and Simpson, B. R. (1973). A new muscle relaxant—AH 8165 *Proc. R. Soc. Med.*, **66**, 1023

Bonta, I , Goorissen, E. M., and Derkx, F H (1968) Pharmacological interaction between pancuronium and anaesthetics. *Eur. J. Pharmacol.*, **4**, 83

Booij, L H. D. J., Edwards, R. P., Sohn, Y. J., and Miller, R. D (1980) Cardiovascular and neuromuscular effects of Org NC 45, pancuronium, metocurine and d-tubocurarine in dogs. *Anesth. Analg. (Cleve.)*, **59**, 26.

Bowman, W. C. (1980). *Pharmacology of Neuromuscular Function with Special Reference to Anaesthetic Practice.* Bristol: John Wright & Sons (in press).

Brittain, R. T., and Tyers, M. B (1973). The pharmacology of AH 8165: a rapid acting, short lasting, competitive neuromuscular blocking drug. *Br. J. Anaesth.*, **45**, 837.

Brown, B. B., and Crout, J. R. (1970). The sympathomimetic effect of gallamine on the heart. *J. Pharmacol. Exp. Ther* , **172**, 266.

Buckett, W. R., and Frisk-Holmberg, M. (1970). The use of neuromuscular blocking agents to investigate receptor structure requirements for histamine release. *Br. J. Pharmacol.*, **40**, 165P.

—— Marjoribanks, C. E. B., Marwick, F. A., and Morton, M. B (1968). The pharmacology of pancuronium bromide (Org NA 97), a new potent steroidal neuromuscular blocking agent *Br. J Pharmacol. Chemother.*, **32**, 671

Clanachan, A. S., and McGrath, J. C. (1976) Effects of ketamine on the peripheral autonomic nervous system of the rat. *Br. J. Pharmacol.*, **58**, 247.

Clark, A. L , and Mitchelson, F. (1976). The inhibitory effect of gallamine on muscarinic receptors. *Br. J. Pharmacol.*, **58**, 323.

Coleman, A. J., Downing, J. W., Leary, W. P , Moyes, D. G , and Styles, M. (1972). The immediate cardiovascular effects of pancuronium, alcuronium and tubocurarine in man. *Anaesthesia*, **27**, 415.

Comroe, J. H., and Dripps, R. D. (1946). The histamine-like action of curare and tubocurarine injected intracutaneously and intra-arterially in man. *Anesthesiology*, **7**, 260

Docherty, J R., and McGrath, J. C. (1978). Sympathomimetic effects of pancuronium bromide on the cardiovascular system of the pithed rat; a comparison with the effects of drugs blocking the neuronal uptake of noradrenaline. *Br. J. Pharmacol.*, **64**, 589.

———— (1980). A comparison of the relaxant and autonomic effects of pancuronium and its monoquaternary derivative Organon NC 45 in the pithed rat. *Br. J. Pharmacol.*, **68**, 140P.

Domenech, J. S , Garcia, R. C., Sasiain, J. M. R., Loyola, A. Q., and Oroz, J. S. (1976) Pancuronium bromide. an indirect sympathomimetic agent. *Br. J. Anaesth.*, **48**, 1143.

Durant, N. N. (1978). A comparison, in the anaesthetised cat and monkey, of pancuronium with a monoquaternary analogue. Proc Vth Eur Congr Anaesth, Paris. *Excerpta Med.*, **452**, 240

—— Bowman, W. C., and Marshall, I. G. (1977). A comparison of the neuromuscular and autonomic blocking activities of (+)-tubocurarine and its N-methyl and O,O,N-trimethyl analogues. *Eur. J. Pharmacol.*, **46**, 297.

—— Marshall, I. G., Savage, D. S., Nelson, D. N., Sleigh, T., and Carlyle, I. C. (1979). The neuromuscular and autonomic blocking activities of pancuronium analogues in the cat. *J Pharm. Pharmacol.*, **31**, 831

Ertama, P. M. (1978). Histamine release in rats after administration of five neuromuscular blocking agents. *Arch. Int. Pharmacodyn. Ther.*, **233**, 82.

Gandiha, A., Marshall, I. G , Paul, D., Rodger, I. W., Scott, W., and Singh, H. (1975). Some actions of chandonium iodide, a new short-acting muscle relaxant, in anaesthetised cats and on isolated muscle preparations *Clin. Exp. Pharmacol. Physiol.*, **2**, 159.

Gillespie, J. S., MacLaren, A., and Pollock, D. (1970). A of stimulating different segments of the autonomic rom the spinal column to various organs in the pithed cat and rat. *Br. J. Pharmacol.*, **40**, 257.

Guyton, A. C., and Reeder, R. C (1950). Quantitative studies on the autonomic actions of curare. *J. Pharmacol. Exp. Ther.*, **98**, 188.

Hughes, R., and Chapple, D. J. (1976). Effects of non-depolarizing neuromuscular blocking agents on peripheral autonomic mechanisms in cats. *Br. J. Anaesth* , **48**, 59.

Hume, W R., De la Lande, I. S , and Waterson, J. G. (1972) Effect of acetylcholine on the response of the isolated rabbit ear artery to stimulation of the perivascular sympathetic nerves. *Eur. J. Pharmacol.*, **17**, 227.

Ivankovich, A. D., Miletich, D. J., Albrecht, R. F., and Zahed, B (1975). The effect of pancuronium on myocardial contraction and catecholamine metabolism. *J. Pharm. Pharmacol.*, **27**, 837.

Johnstone, M., Mahmoud, A. A., and Mrozinsky, R. A. (1978). Cardiovascular effects of tubocurarine in man. *Anaesthesia*, **33**, 587.

Kelman, G. R., and Kennedy, B. R. (1971). Cardiovascular effects of pancuronium in man. *Br. J. Anaesth.*, **43**, 335.

Kennedy, B. R , and Kelman, G R. (1970). Cardiovascular effects of alcuronium in man *Br. J. Anaesth.*, **42**, 625.

Li, C. K., and Mitchelson, F. (1978). The effect of stercuronium on cardiac muscarinic receptors. *Eur J. Pharmacol.*, **51**, 251.

MacIntosh, F C., and Paton, W. D. M. (1949) The liberation of histamine by certain organic bases. *J. Physiol (Lond.)*, **109**, 190.

MacLagan, J. (1976). Competitive neuromuscular blocking drugs; in *Neuromuscular Junction* (ed. E. Zaimis), p. 421. Berlin Springer-Verlag

Marshall, I. G. (1973). The ganglion blocking and vagolytic actions of three short-acting neuromuscular blocking drugs in the cat. *J Pharm. Pharmacol.*, **25**, 530.

—— (1980). Actions of non-depolarising neuromuscular blocking agents at cholinoceptors other than at the motor endplate. Proc. XIth Internatl Meeting of Anaesthesia and Intensive Care, Paris. *Excerpt. Med.*, (in press).

—— Agoston, S., Booij, L. H. D. J., Durant, N. N., and Foldes, F. F. (1980). Pharmacology of Org NC 45 compared with other non-depolarizing neuromuscular blocking drugs. *Br. J. Anaesth.*, **52**, 11S.

Marshall, R. J., and Ojewole, J. A. O. (1979). Comparison of the autonomic effects of some currently used neuromuscular blocking agents. *Br. J. Pharmacol.*, **66**, 77P.

Nana, A., Cardan, E., and Domokos, M. (1973). Blood catecholamine changes after pancuronium. *Acta Anaesthesiol. Scand.*, **17**, 83.

Rand, M. J., and Varma, B. (1970). Effects of cholinomimetic drugs on responses to sympathetic nerve stimulation and noradrenaline in the rabbit ear artery. *Br. J. Pharmacol.*, **38**, 758.

Randall, L. O. (1951). Synthetic curare-like agents and their antagonists. *Ann. N.Y. Acad. Sci.*, **54**, 460.

Rathbun, F. J., and Hamilton, J. T. (1970). Effect of gallamine on cholinergic receptors. *Can. Anaesth. Soc. J.*, **17**, 574.

Riker, W. F., and Wescoe, W. C. (1951). The pharmacology of Flaxedil with observations on certain analogs. *Ann. N.Y. Acad. Sci.*, **54**, 373.

Salt, P. J., Barnes, P. K., and Conway, C. M. (1980). Inhibition of neuronal uptake of noradrenaline in the isolated perfused rat heart by pancuronium and its homologues. Org 6368, Org 7268, and Org NC 45. *Br. J. Anaesth.*, **52**, 313.

Savege, T. M., Blogg, C. G., Ross, L., Lang, M., and Simpson, B. R. (1973). The cardiovascular effects of AH 8165, a new non-depolarising muscle relaxant. *Anaesthesia*, **28**, 253.

Saxena, P. R., and Bonta, I. L. (1970). Mechanism of selective cardiac vagolytic action of pancuronium bromide. Specific blockade of cardiac muscarinic receptors. *Eur. J. Pharmacol.*, **11**, 332.

Shepherd, J. T., Lorenz, R. R., Tyce, G. M., and Vanhoutte, P. M. (1978). Acetylcholine-inhibition of transmitter release from adrenergic nerve terminals mediated by muscarinic receptors. *Fed. Proc.*, **37**, 191.

Smith, N. T., and Whitcher, C. E. (1967). Hemodynamic effects of gallamine and tubocurarine administered during halothane anesthesia. *J.A.M.A.*, **199**, 704.

Steinsland, O. D., Furchgott, R. F., and Kirkepar, S. M. (1973). Inhibition of adrenergic neurotransmission by parasympathomimetics in the rabbit ear artery. *J. Pharmacol. Exp. Ther.*, **184**, 346.

Stoelting, R. K. (1972). The hemodynamic effects of pancuronium and d-tubocurarine in anesthetised patients. *Anesthesiology*, **36**, 612.

Thomas, E. T. (1957). The effect of d-tubocurarine chloride on the blood pressure of anaesthetised patients. *Lancet*, **2**, 772.

Tomlinson, D. R. (1979). On the mechanism of pancuronium-induced supersensitivity to noradrenaline in rat smooth muscle. *Br. J. Pharmacol.*, **65**, 473.

Vanhoutte, P. M. (1977). Cholinergic inhibition of adrenergic transmission. *Fed. Proc.*, **36**, 2444.

Vercruysse, P., Bossuyt, P., Hanegreefs, G., Verbeuren, T. J., and Vanhoutte, P. M. (1979). Gallamine and pancuronium inhibit pre- and postjunctional muscarinic receptors in canine saphenous veins. *J. Pharmacol. Exp. Ther.*, **209**, 225.

Waud, D. R., Lee Son, S., and Waud, B. E. (1978). Kinetic and empirical analysis of dose–response curves illustrated with a cardiac example. *Life Sci.*, **22**, 1275.

COMPARAISON DES ACTIONS CARDIOVASCULAIRES D'ORG NC 45 ET DE CELLES PRODUITES PAR D'AUTRES AGENTS NEUROMUSCULAIRES NON DEPOLARISANTS EFFECTUEE SUR DES ANIMAUX EXPERIMENTAUX

RESUME

Les actions cardiovasculaires de 1-[(2β,3α,16β,17β)-3,17-bis(acétyloxy)-2-(1-piperidinyl)-androstan-16-y1]-1-méthyl-bromure de piperidinium (Org NC 45) sont revues et comparées à celles d'autres agents de blocage neuromusculaire non dépolarisants. Les résultats obtenus sur des chats et des chiens anesthésiés ont prouvé que, contrairement aux autres agents de blocage neuromusculaire, Org NC 45, même en doses 20 fois plus fortes que celles requises pour les blocages neuromusculaires, n'a aucun effet sur la fréquence cardiaque, la pression artérielle, les ganglions autonomes et l'activité adrénoceptrice ou baroceptrice. Les études effectuées sur des rats énervés et sur des oriellettes de cochons d'Inde ont également montré qu'Org NC 45 n'a que peu d'effet sur les récepteurs muscariniques cardiaques ou sur les mécanismes de refixation de la noradrénaline. Ces résultats laissent penser qu'Org NC 45 possède des avantages significatifs par rapport aux agents de blocage neuromusculaire non dépolarisants utilisés actuellement, du fait que son usage clinique n'a pas à être associé à des effets secondaires cardiovasculaires.

VERGLEICH DER KARDIOVASKULÄREN AKTIONEN VON ORG NC 45 MIT JENEN, DIE VON ANDEREN NICHT-DEPOLARISIERENDEN NEUROMUSKULÄREN MITTELN IN TIERVERSUCHEN HERVORGERUFEN WERDEN

ZUSAMMENFASSUNG

Die Kardiovaskulären Aktionen von 1-[(2β,3α,5α,16β,17β)-3,17-bis(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methyl-3-piperidinium bromide (Org NC 45) werden überprüft und mit denen von anderen nicht-depolarisierenden neuromuskulären Blockierungsdrogen verglichen. Resultate an narkotisierten Katzen und Hunden haben gezeigt, dass die neue Droge im Gegensatz zu anderen neuromuskulären Blockierungsdrogen selbst in Dosen, die 20 × grosser sind als für eine neuromuskuläre Blockierung erforderlich, keine Auswirkung auf die Herztätigkeit, den arteriellen Druck, die autonomen Ganglien und die Aktivität von Adreno- und Barorezeptoren hat. Untersuchungen bei Ratten und Meerschweinchen haben weiter gezeigt, dass Org NC 45 kaum Auswirkungen auf die Herz-Muskarin-Rezeptoren oder auf den Wiederaufnahmemechanismus fur Noradrenalin hat. Diese Resultate zeigen, dass Org NC 45 wesentliche Vorteile gegenuber gegenwartig verwendeten nicht-depolarisierenden neuromuskularen Blockierungsdrogen hat, da seine klinische Verwendung nicht mit kardiovaskularen Nebenerscheinungen in Verbindung gebracht werden sollte.

COMPARACION DE LAS ACCIONES CARDIOVASCULARES DEL ORG NC 45 CON LAS PRODUCIDAS POR OTROS AGENTES NEUROMUSCULARES NO DESPOLARIZANTES EN EXPERIMENTOS CON ANIMALES

SUMARIO

Las acciones cardiovasculares del Org NC 45, 1 - [(2β,3α,5α,16β,17β) - 3,17-bis(acetiloxia) - 2 - (1-piperidinilo) - andostran-16-ilo]-1-bromuro de piperidinium de metilo, se revisan y comparan con las de otras drogas de bloqueo neuromuscular y no despolarizantes. Los resultados obtenidos en perros y gatos anestesiados han demostrado que, en contraposición a otras drogas de bloqueo neuromuscular, el Org NC 45 no ejerce efecto alguno en el ritmo del corazón, presión arterial, ganglia autonómica, ni en la actividad de los baroreceptores o adrenoceptores. Los estudios efectuados en el atrium de ratas y animales de laboratorio han mostrado que el Org NC 45 ejerce un efecto muy reducido en los receptores muscarínicos cardiacos y en los mecanismos de reabsorción de noradrenalina. Estos resultados sugieren que el Org NC 45 posee ventajas significativas sobre las drogas no despolarizantes de bloqueo neuromuscular que actualmente se encuentran en uso, puesto que su uso clínico no debiera asociarse con los efectos cardiovasculares secundarios.

Br. J. Anaesth. (1980), **52**, 33S

PRELIMINARY REVIEW OF THE INTERACTIONS OF ORG NC 45 WITH ANAESTHETICS AND ANTIBIOTICS IN ANIMALS

N. Krieg, J. M. J. Rutten, J. F. Crul and L. H. D. J. Booij

SUMMARY

In vitro (rat hemidiaphragm) and *in vivo* (rat and cat tibialis anterior muscle preparation) studies of the interactions between Org NC 45 and some i.v. anaesthetics and antibiotics were carried out. With the exception of ketamine 1 mg kg^{-1} none of the drugs tested *in vivo* significantly changed the time course of an Org NC 45 bolus injection. All of the drugs caused an enhancement of the neuromuscular block using infusions *in vivo* and also in the *in vitro* preparations. Org NC 45 seems to be potentiated in a manner similar to pancuronium.

Some i.v. anaesthetic drugs and some antibiotics impair neuromuscular transmission and consequently may potentiate neuromuscular blocking drugs, giving rise to effects which may be of clinical importance (Pittinger, Eryasa and Adamson, 1970; Amaki et al., 1978; Burkett et al., 1979). We have therefore studied the potential interactions between the new non-depolarizing neuromuscular blocking drug Org NC 45 and a number of i.v. anaesthetics and antibiotics. Some preliminary results of these interaction studies are described in this review. We chose for the study those anaesthetics which are commonly used as sole anaesthetics in high doses. Recently, fentanyl had been used in the same way (Stanley and Webster, 1978) and therefore this drug was included. In the study of antibiotics we tested those which were seen to influence the potency of pancuronium in clinical doses (Crul et al., 1979).

METHODS

In vitro *experiments*

Isolated rat phrenic nerve-hemidiaphragm preparations (Bülbring, 1946) were suspended in Krebs–Henseleit solution (Krebs and Henseleit, 1932). The solution was gassed with 5% carbon dioxide in oxygen and maintained at 37 °C. The stimulation techniques and recording of the twitch response used were those described by Crul–Sluyter and Crul (1974) using supramaximal twitch stimuli of 0.2 ms duration applied every 10 s to the phrenic nerve.

In the anaesthetic studies, Org NC 45 was first added to the preparations to produce a concentration of 4 $\mu g\ ml^{-1}$. This caused $35 \pm 4\%$ twitch depression (mean ± SEM, $n = 20$). When a constant partial block was achieved, incremental doses of anaesthetic drugs were added and their effects were noted. In control experiments, i.v. anaesthetics were added to the preparations in the absence of Org NC 45.

In the antibiotic interaction studies, the antibiotics were added to the organ bath in concentrations which did not effect twitch tensions by themselves. Org NC 45 or pancuronium bromide were then added in cumulative incremental doses. Dose-response curves for each neuromuscular blocking drug in the presence or absence of antibiotic were constructed using linear regression analysis to calculate the lines of best fit.

In vivo *Experiments*

Cats weighing 2.6–3.9 kg were anaesthetized with pentobarbitone 45 mg kg^{-1} and rats weighing 280–410 g with pentobarbitone 40 mg kg^{-1} and urethane 100 mg kg^{-1} i.p. The animals were artificially ventilated with 30% oxygen in nitrous oxide and their body temperatures maintained between 37 and 38 °C by means of heating pads. The end expiratory carbon dioxide concentration was kept constant between 3.2 and 3.5 vol%. Stimuli of supramaximal amplitude (duration 0.2 ms, frequency 0.1 Hz) were applied to the sciatic nerve and the isometric twitch response of the tibialis anterior muscle was recorded (Crul–Sluyter and Crul, 1974). Two types of

---

Norbert Krieg, M.D.; Jan M. J. Rutten, M.D.; Jan F. Crul, M.D. Ph.D.; Leo H. D. J. Booij, M.D.; Department of Anaesthesiology, Catholic University, St Radboud Hospital, Geert Groote Plein Zuid 12, Nijmegen, The Netherlands.

Reprint requests to N. K

0007–0912/80/130033–04 $01.00

© Macmillan Publishers Ltd 1980

experiments were performed. In one a constant degree of block (at least 15 min duration at about 50% twitch depression) was produced by an i.v. infusion of Org NC 45 and the effects of i.v. bolus doses of anaesthetics or antibiotics were determined. In the second the time-courses of blocks produced by the bolus injections of Org NC 45 2.4 mg kg^{-1} in rats and 0.4 mg kg^{-1} in cats for the anaesthetic studies and of 0.5 mg kg^{-1} in rats and 0.05 mg kg^{-1} in cats for the antibiotics studies, were compared in rats and cats pretreated with i.v. anaesthetics or antibiotics, or in their absence.

Student's t test was used to assess the significance of the results.

The drugs used were clindamycin, neomycin, gentamicin, etomidate, ketamine, fentanyl and gammahydroxybutyrate.

RESULTS

I.v. anaesthetics

Isolated rat hemidiaphragm. Ketamine and etomidate added in incremental concentrations produced a dose-dependent increase in the amplitude of the indirectly-evoked twitches, whereas gammahydroxybutyrate produced a dose-dependent depression. Fentanyl was without effect on the twitch. When the same drugs were added during an approximately 35% reduction in twitch tension produced by Org NC 45 4 µg ml^{-1}, they all enhanced the block in a dose-dependent manner. The results are summarized in table I.

TABLE I. *Effect of i.v. anaesthetic drugs on the indirectly evoked twitch of the rat hemidiaphragm without Org NC 45 and on a 35% twitch depression produced by a bath concentration of Org NC 45 4 µg ml^{-1} (means ± SEM)*

	Δ%Twitch force	
Drug	Drug alone	With Org NC 45
Ketamine		
1 µg ml^{-1}	+1.2±0 8	−5.4±1.0
5 µg ml^{-1}	+5.0±1 2	−26 1±2 6
10 µg ml^{-1}	+9.3±1.9	−70 3±3.9
Fentanyl		
0.1 µg ml^{-1}	+1.9±1.8	−21.0±1.2
0.25 µg ml^{-1}	+1.1±2.1	−28.8±1.6
0 35 µg ml^{-1}	−1.2±3.7	−61.1±1 5
Gammahydroxybutyrate		
500 µg ml^{-1}	−5.2±0 5	−5.8±0.2
1500 µg ml^{-1}	−15.0±1.5	−17.3±0.8
3500 µg ml^{-1}	−31.8±2.8	−44 6±1.2
Etomidate		
5 µg ml^{-1}	+2.9±1.1	−8.8±1.8
10 µg ml^{-1}	+6.1±1.1	−25.0±4.9
20 µg ml^{-1}	+12.4±3.8	−56.7±6.6

Anaesthetized cats and rats. When injected during an approximately 50% depression of the cat tibialis anterior muscle maintained by a continuous i.v. infusion of Org NC 45, fentanyl 0.01 mg kg^{-1}, gammahydroxybutyrate 60 mg kg^{-1}, etomidate 0.3 mg kg^{-1} and ketamine 1 mg kg^{-1} each produced an additional depression of twitch tension of about 25% (mean ± SEM = 25 ± 3%). The effect appeared to be least with fentanyl and greatest with ketamine but, statistically, there were no differences between the effects of the drugs at these doses.

In cats or rats given a bolus dose of an anaesthetic (ketamine 1 mg kg^{-1}; gammahydroxybutyrate 60 mg kg^{-1}; etomidate 0.3 mg kg^{-1}) or of fentanyl 0.01 mg kg^{-1}, the recovery indices (the time for recovery from 25 to 75% twitch tension) of a subsequent bolus dose of Org NC 45 given 10 min later were not different from those of control animals not pretreated with the anaesthetics, apart from ketamine which significantly prolonged the time of recovery from 25 to 75% of control twitch tension by 1.8-fold in the cat and 1.4-fold in the rat ($P < 0.05$).

Antibiotics

Isolated rat hemidiaphragm. Dose–response curves for both Org NC 45 and pancuronium were determined in the absence or in the presence of neomycin 160 µg ml^{-1}. Neomycin, in this dose, was itself without effect on the twitch of the diaphragm, but caused a shift to the left of the dose–response curves for pancuronium and Org NC 45 (fig. 1). Neomycin potentiated both blocking drugs by similar amounts. At the concentrations required to produce a 50% twitch block, pancuronium was potentiated by 1.53-fold and Org NC 45 by 1.58-fold.

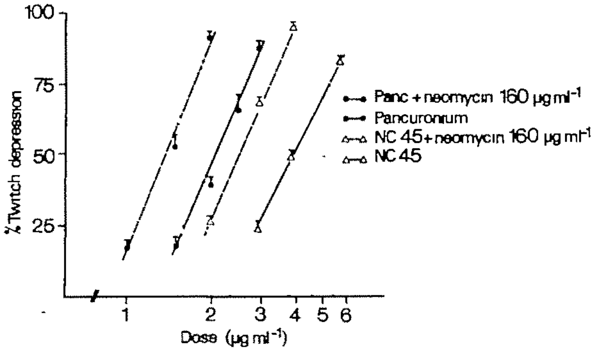


FIG. 1. Influence of a threshold dose of neomycin 160 µg ml^{-1} on the dose–response curve of Org NC 45 and pancuronium in the rat hemidiaphragm.

Anaesthetized cats and rats. When a bolus injection of neomycin, gentamicin or clindamycin was given during an approximately 50% twitch block maintained by a continuous infusion of Org NC 45 in the cat or rat, an additional twitch depression was produced. The results are summarized in table II. The potentiation appeared greater in the cat than in the rat, although such a difference could be accurately determined only if the slopes of dose-response curves to Org NC 45 in the two species were known.

When a bolus dose of neomycin (up to 3 mg kg^{-1}), gentamicin (up to 1 mg kg^{-1}) or clindamycin (up to 10 mg kg^{-1}) was injected 5 min before a 95% blocking bolus dose of Org NC 45 (0.5 g kg^{-1} in the rat and 0.05 g kg^{-1} in the cat) the depth and the time-course of the paralysis produced by Org NC 45 were not different from those of control cats or rats ($P<0.05$) given only the bolus injection of Org NC 45.

TABLE II. *Effects of antibiotics on a 50% twitch depression produced* in vivo *by Org NC 45 in the rat and the cat. Each antibiotic was given as a single bolus i.v. injection. Values are means ± SEM*

Drug	Dose (mg kg^{-1})	% Block			
		Rat	*n*	Cat	*n*
Clindamycin	10	−4.6±2.7	4	−14.0±3.5	5
Gentamicin	1	−11.3±2.0	8	−20.3±5.2	5
Neomycin	3	−15.9±3.3	7	−26.7±2.1	4

DISCUSSION

The results show that the neuromuscular block produced by Org NC 45 is potentiated by some i.v. anaesthetics and antibiotics as are pancuronium and tubocurarine (Amaki et al., 1978; Burkett et al., 1979). The effects were most easily demonstrable *in vitro* and in those *in vivo* experiments in which continuous infusions of Org NC 45 were given. The explanation for this result might be that there is a dynamic equilibrium between the concentrations of blocking drug at the neuromuscular junction and in the plasma during continuous infusion under conditions of stable partial block. Such preparations seem to be highly sensitive to combinations of drugs. With the exception of ketamine, neither the anaesthetic agents nor fentanyl altered the time-course of the effect of a bolus dose of Org NC 45 administered subsequently. The antibiotics administered in doses comparable to those used clinically, were also without effect in this type of experiment. The results show that similar interactions with anaesthetic drugs and antibiotics may be expected with Org NC 45 as with other non-depolarizing drugs.

ACKNOWLEDGEMENTS

The authors are thankful to Francien v. d. Pol, Michel Knol and Wim Kleinhans for help.

REFERENCES

Amaki, Y., Nagashima, H., Radnay, P. A., and Foldes, F. F. (1978). Ketamine interaction with neuromuscular blocking agents in the phrenic nerve–hemidiaphragm preparation of the rat. *Anesth. Analg.* (*Cleve.*), 57, 238

Bülbring, E. (1946). Observations on the isolated phrenic nerve–diaphragm preparation of the rat. *Br. J. Pharmacol.*, **1**, 38.

Burkett, L., Bikhazi, G. B., Kelly, C. T., Desiree, A. R., Wirta, M. G. and Foldes, F. F. (1979). Mutual potentiation of the neuromuscular effects of antibiotics and relaxants *Anesth. Analg.* (*Cleve.*), **58**, 107.

Crul, J. F., Booij, L. H. D. J., Rutten, J. M. J., De Groot, A., Rutten, Ch., and Van der Pol, F. (1979). Interaction of antibiotics and muscle relaxants in abdominal surgery; in *Intra-abdominal Sepsis*, proceedings of a symposium held in Nijmegen (ed. H. H. M. de Boer), p. 9. Utrecht: Bunge Scientific Publisher.

Crul–Sluyter, E. J., and Crul, J. F. (1974). Acidosis and neuromuscular blockade. *Acta Anaesthesiol. Scand.*, **18**, 224.

Krebs, M. A., and Henseleit, K. (1932). Untersuchungen über die Harnstoffbildung im Tierkörper. *Hoppe-Seyler's Z. Physiol. Chem.*, **210**, 33.

Pittinger, C. B., Eryasa, Y., and Adamson, R. (1970) Antibiotic induced paralysis. *Anesth. Analg.* (*Cleve.*), **49**, 487.

Stanley, T. H., and Webster, L. R. (1978). Fentanyl–oxygen anaesthesia for patients with mitral valve disease; in *Stress-Free Anaesthesia*, The Royal Society of Medicine, Int. congress and symposium Series number 3, p. 27. London: Academic Press.

REVUE PRELIMINAIRE DE L'INTERACTION ENTRE ORG NC 45 ET DES AGENTS ANESTHESIANTS ET ANTIBIOTIQUES SUR DES ANIMAUX

RESUME

On a procédé à certaines études portant sur l'interaction entre Org NC 45 et certains agents anesthésiants et antibiotiques administrés par voie intraveineuse, en utilisant des préparations d'hémi-diaphragme de rat *in vitro* et de muscle tibial antérieur de rat et de chat *in vivo*. A l'exception de la kétamine (1 mg kg^{-1}), aucun des médicaments soumis aux essais *in vivo* n'a modifié d'une manière significative la durée d'action de l'injection d'un bol d'Org NC 45. Tous ces médicaments ont provoqué une stimulation du blocage neuromusculaire lorsqu'on a utilisé des infusions *in vivo*, et il en a été de même dans les préparations *in vitro*. Org NC 45 semble agir d'une manière similaire au pancuronium.

VORLÄUFIGER ÜBERBLICK ÜBER WECHSELWIRKUNGEN VON ORG NC 45 MIT NARKOSEMITTELN UND ANTIBIOTIKA BEI TIEREN

ZUSAMMENFASSUNG

Studien *in vitro* (Ratten-Hemidiaphragma) und *in vivo* (Ratten u. Katzen-Muskelpraparate des Tibialis anterior) der Wechselwirkungen zwischen Org NC 45 und einigen intravenös gegebenen Narkosemitteln und Antibiotika wurden durchgefuhrt. Mit Ausnahme von Ketamin (1 mg kg^{-1}) veränderte keine der *in vivo* getesteten Drogen wesentlich den Wirkungsablauf einer Bolusinjektion von Org NC 45. Alle Drogen bewirkten eine Verstärkung der neuromuskularen Blockierung mit Infusionen *in vivo* und auch in den *in vitro*-Praparaten Org NC 45 scheint ahnliche Wirkungen wie Pancuronium zu haben.

REVISION PRELIMINAR DE LAS INTERACCIONES DE ORG NC 45 CON ANESTESICOS Y ANTIBIOTICOS EN ANIMALES

SUMARIO

Se efectuaron estudios *in vitro* (hemidiafragma) e *in vivo* (preparación tibialis del músculo anterior de rata y gato) de las interacciones entre el Org NC 45 y algunos anestésicos y antibióticos intravenosos. A excepción de la ketamina (1 mg kg^{-1}), ninguna de las drogas verificadas *in vivo* cambiaron significativamente la acción en el tiempo de una inyección de Org NC 45 Todas las demás drogas ocasionaron un resurgir del bloqueo neuromuscular, al usar infusiones *in vivo*, y también en las preparaciones *in vitro*, el Org NC 45 parece estar potenciado de manera similar al pancuronium.

Br. J. Anaesth. (1980), **52**, 37S

PHARMACOKINETICS AND PHARMACODYNAMICS OF ORG NC 45 IN MAN

F. VAN DER VEEN AND A. BENCINI

SUMMARY

A combined pharmacokinetic–pharmacodynamic study of Org NC45 was performed in six patients undergoing elective oro–facial surgery. The pharmacokinetics could be described using a two-compartment open model with a distribution half-life of approximately 4 min and an elimination half-life of approximately 31 min. The pharmacokinetic parameters confirm earlier clinical findings that Org NC 45 has a more rapid onset and a shorter duration of action than pancuronium, and a faster recovery rate. When comparing the pharmacokinetic and pharmacodynamic parameters the biophase could be distinguished from both the central and the peripheral compartments. The mean steady-state plasma concentration producing a 50% block of the twitch response was 0.137 µg ml^{-1} (range 0.118–0.176 µg ml^{-1}).

Org NC 45 has been shown to be a short-acting non-depolarizing neuromuscular blocking drug with a wide margin of safety. It is virtually devoid of vagolytic activity in animals (Marshall et al., 1980). Preliminary clinical trials showed it to act faster than pancuronium and to have a faster recovery rate. In order to establish dose regimes for bolus injections and constant infusion regimes we report here a combined pharmacokinetic and dynamic study performed in six patients undergoing oro–facial surgery. The pharmacokinetic study was based on a specific assay developed for Org NC 45 which excluded its hydrolysis or metabolic products (J. E. Paanakker and G. Van de Laar, in preparation).

METHODS

Informed consent was obtained from the six patients undergoing facial or oral surgery who participated in the study. Details of the patients and of the doses of Org NC 45 used are given in table I.

One hour before surgery droperidol 5 mg i.m. and atropine 0.5 mg i.m. were given. Anaesthesia was induced with droperidol 15 mg i.v. or diazepam 10 mg i.v. with fentanyl 0.2 mg i.v. and either etomidate 18 mg i.v. or thiopentone 100 mg i.v. Anaesthesia was maintained using nitrous oxide (66%) in oxygen supplemented with additional doses of droperidol and fentanyl. Four patients (A, D, F and G) were given suxamethonium to facilitate endotracheal intubation.

Small stainless-steel needle electrodes were placed in the left forearm and the ulnar nerve was stimulated using a supramaximal voltage at 0.1 Hz (Grass S 48 stimulator and SIU 5 isolation unit). The evoked twitch contraction of the adductor pollicis muscle was recorded using a Statham VC3 Gold cell linear force transducer attached to a Brush Clevite recorder. The maximum effect of Org NC 45, the duration of action and the recovery rate were measured.

Org NC 45 was given initially as a rapid bolus injection of 0.089–0.12 mg kg^{-1} via an antecubital vein in the right forearm. In four patients (A, F, G and H) a constant infusion of between 1.2 and 1.51 µg kg^{-1} min^{-1} was given via the same vein for periods of between 80 and 202 min.

Venous blood samples (8 ml) were taken at predetermined times from an indwelling catheter in another vein. These samples, mixed with citrate as an anticoagulant, were centrifuged immediately and the volume and pH measured immediately after centrifugation. The pH of the sample was adjusted to approximately 6 units using a sodium phosphate buffer to prevent the hydrolysis of Org NC 45 which occurs at physiological pH. The plasma concentrations of Org NC 45 were determined using a selective high performance liquid chromatographic (HPLC) assay which used ion-pair extraction and straight-phase adsorption

---

F. VAN DER VEEN, Scientific Development Group, Organon International B.V., Oss, The Netherlands. A. BENCINI, M.D., Department of Anaesthesia. University of Groningen, Groningen, The Netherlands.

Correspondence to F. van der Veen.

0007-0912/80/130037-05 $01.00

© Macmillan Publishers Ltd 1980

TABLE I. *Patient data and dosing schedules. †Irregular dose rate at the start of the infusion (1.013–2.039 μg min^{-1} during the first 64 min). *Patients given suxamethonium to facilitate endotracheal intubation*

Patient	Sex	Age (yr)	I.v. bolus dose (mg kg^{-1})	I v. infusion data		
				Dose rate (μg kg^{-1} min^{-1})	Started (min)	Stopped (min)
D*	F	65	0.105			
J	M	25	0.111			
A*	M	28	0.108	1.2	31.0	124
F*	F	33	0.089	1.42	22.7	147
G*	M	21	0.104	1.46†	20.5	223
H	F	22	0.111	1.51	21.5	100

chromatography (J. E. Paanakker and G. Van de Laar, in preparation). The accuracy and precision of this method were 0.7 and 2.8% respectively. Org NC 58 (17-OH Org NC 45) was used as an internal standard after initial experiments showed it not to be present in plasma samples following the i.v. administration of Org NC 45.

Pharmacokinetic and pharmacodynamic modelling

A linear two-compartment open model with injection into and elimination from the central compartment was used to describe the time-course of plasma concentrations of Org NC 45 following the bolus injection and the constant infusions (Hull, 1979). The concentration of drug in the central compartment (C_1) as a function of time is given by

$$C_1 = A_0 e^{-\alpha t} + B_0 e^{-\beta t}$$

Where α and β are the rate constants for the distribution and elimination phases and A_0 and B_0 the extrapolated theoretical concentrations at zero time for the two phases.

From these "functional" parameters the following "model" parameters were calculated (Hull, 1979):

k_{12} = the rate constant from the central to the peripheral compartment,
k_{21} = the rate constant from the peripheral to the central compartment,
k_{10} = the rate constant from the central compartment to the outside (the elimination constant),
V_1 = the volume of the central compartment,
V^{ss} = the steady-state volume of distribution.

For the subsequent modelling of the pharmacodynamic response, the two-compartment model was extended to include a hypothetical effect compartment (Sheiner et al., 1979). Drug is tranferred to this effect compartment from the central compartment. The mathematical expression describing the neuromuscular blocking effect (E) is given by

$$E = \frac{(k_{eo}Z)^{\gamma}}{(k_{eo}Z)^{\gamma} + C_p^{ss}(50)^{\gamma}}$$

where k_{eo} = rate constant from the effect compartment to outside; $C_p^{ss}(50)$ = the plasma concentration at a steady state which produces 50% of the maximal effect; Z = a function of the pharmacokinetic parameters and time and γ = a parameter for the sigmoid relationship between the effect and the drug concentration in the effect compartment.

The steady-state plasma concentration eliciting any value of the effect E between zero and unity (maximal effect) ($C_p^{ss}(E)$) can be calculated:

$$C_p^{ss}(E) = C_p^{ss}(50)\left\{\frac{E}{1-E}\right\}^{1/\gamma}$$

The curve-fitting and the solution of the necessary equations were performed using non-linear least square regression analyses by a Fortran IV computer program based on a random search algorithm.

RESULTS

Following the administration of an i.v. bolus complete neuromuscular block was produced after an average onset time of 2.7 min. The plasma concentrations showed a rapid initial decline followed by a more gradual decline (fig. 1). In four of the patients a continuous infusion was started during the recovery phase from the bolus dose. After stopping the infusion there was a rapid recovery of normal neuromuscular transmission (fig. 2). The constant infusions produced increases in the plasma concentrations of the drug

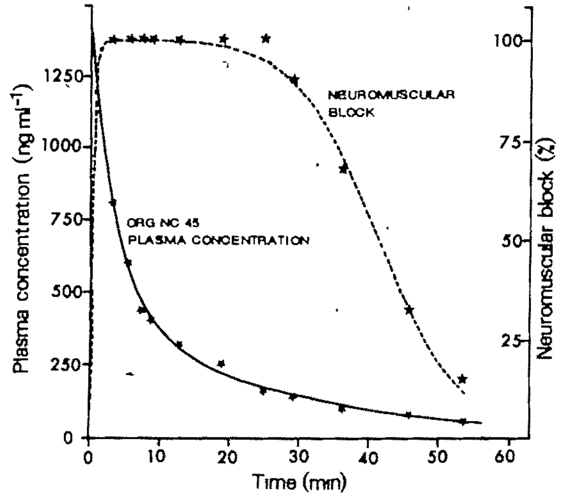


FIG. 1. Plasma concentration of and neuromuscular block produced by a single bolus dose of Org NC 45 0.105 mg kg^{-1}. The solid line is the computer-fitted line describing the decay in concentration and the broken line the computer-fitted line describing the paralysis produced.

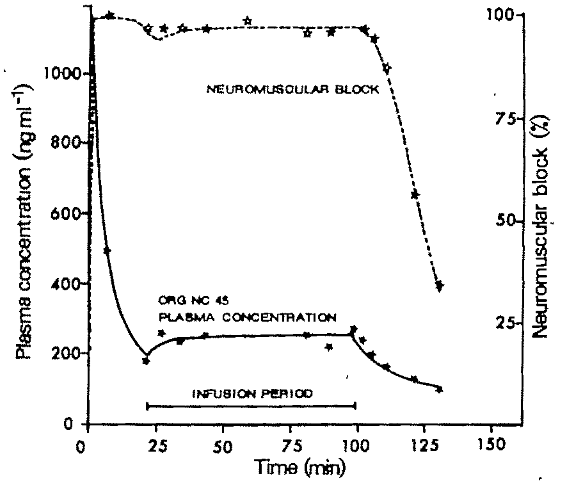


FIG. 2. Plasma concentration of and neuromuscular block produced by a bolus dose of 0.111 mg kg^{-1} followed by an infusion of 1.51 g kg^{-1} min^{-1}. The lines are the computer-fitted lines describing the plasma concentrations and the neuromuscular block.

towards plateau values; following the infusion the plasma concentrations decayed in a bi-exponential fashion (fig. 2). Details of the onset of and recovery from the neuromuscular block are given in table II.

Of the six patients studied two could not be included in the analysis; patient A because it was not possible to use the model to combine the pharmacokinetic and pharmacodynamic data and patient G because the infusion rate was not constant (varying between 1.0 and 2.0 μg kg^{-1} min^{-1}).

TABLE II. *Onset and offset of neuromuscular blockade. *For i.v. bolus: time from injection to 90% recovery; for i.v. bolus+infusion: time after stopping the infusion to 90% recovery. †Subjects given only a bolus injection; the others were given an infusion*

Patient	Onset time (min)	Time interval 25–75% recovery (min)	Duration of action* (min)
D†	2.7	13.9	56
J†	3.0	6.0	36
A	2.0	13.6	64
F	2.3	18.3	40
G	2.9	22.0	27
H	3.1	21.5	45

The kinetic parameters for the remaining four patients are given in table III. The central volume had a mean value of approximately 77 ml kg^{-1}; in physiological terms such a volume is larger than the plasma volume but less than the extracellular fluid volume. The steady-state distribution volume had a mean value of 179 ml kg^{-1} which is almost equivalent to the extracellular fluid volume. The disappearance of drug in the two-compartment model is characterized by two components. The rapid component (the distribution phase) had a mean half-life of 4 min and the slow component (the elimination phase) had a mean half-life of 31 min. Table III also gives the kinetic rate constants.

The dynamic parameters k_{eo}, γ and $C_P^{ss}(50)$ are shown in table IV. The rate constant of elimination of the drug from the effect compartment (k_{eo}) had a mean value of 0.27 min^{-1} (that is a half-life of 2.6 min) and a significantly larger value than that for the transfer of the drug from the peripheral to the central compartment (k_{21} = 0.076 min^{-1}). The model used implies that the "effect" compartment can only be taken to be part of the peripheral compartment if these two constants are not significantly different. The finding that k_{eo} is not very large compared with any of the other rate constants also implies that the effect compartment is not a component of the central compartment.

The mean steady-state plasma concentration giving a 50% depression of the twitch force was 0.137 μg ml^{-1} and that giving a 90% block was 0.206 μg ml^{-1}. Table IV gives the individual estimations.

TABLE III. *Pharmacokinetic parameter estimates of Org NC 45 obtained by* RANDOM SEARCH *computerized curve-fitting. Parameters* A *and* B *are normalized to an i.v. bolus dose of 100 μg kg^{-1}*

Parameter	Subject				Mean ± SD
	D	F	H	J	
Function parameters					
A (μg ml^{-1})	0.900	0.827	0.818	2.311	1.214 ± 0.732
B (μg ml^{-1})	0.423	0.150	0.247	0.412	0.308 ± 0.133
α (min^{-1})	0.26	0.087	0.20	0.44	0.25 ± 0.15
$T_{\frac{1}{2}}^{\alpha}$ (min)	2.7	7.9	3.5	1.6	3.9 ± 2.8
β (min)$^{-1}$)	0.037	0.013	0.019	0.052	0.03 ± 0.018
$T_{\frac{1}{2}}^{\beta}$ (min)	18.5	53.9	36.9	13.3	30.7 ± 18.5
Model parameters					
k_{12} (min^{-1})	0.10	0.030	0.095	0.17	0.10 ± 0.06
k_{21} (min^{-1})	0.11	0.024	0.060	0.11	0 076 ± 0.042
k_{10} (min^{-1})	0.090	0.046	0.062	0.21	0.10 ± 0.07
V_1 (ml kg^{-1})	76	102	94	34	77 ± 29
V^{ss} (ml kg^{-1})	152	228	242	94	179 ± 69

TABLE IV. *Pharmacodynamic parameter estimates of Org NC 45 obtained by* RANDOM SEARCH *computerized curve-fitting*

Parameter	Subject				Mean ± SD
	D	F	H	J	
k_{eo} (min^{-1})	0.19	0.22	0.29	0.36	0.27 ± 0.07
γ	4.3	5.1	5.7	7.7	5.7 ± 1.5
$C_p^{ss}(50)$ (μg ml^{-1})	0.118	0.176	0.131	0.123	0.137 ± 0.027
$C_p^{ss}(90)$ (μg ml^{-1})	0.197	0.271	0.193	0.164	0.206 ± 0.046

DISCUSSION

The results show that a two-compartment open model with injection into and elimination out of the central compartment will describe the disposition of Org NC 45. There was good agreement between the calculated and actual plasma concentrations of the drug and the effects produced.

A comparison of the kinetic and dynamic parameters shows that the biophase can be clearly distinguished from both the central and peripheral compartments. Similar results have been described for tubocurarine (Sheiner et al., 1979).

Only in steady-state conditions is it possible to relate the effect produced to the concentration of drug in the central compartment, for in these conditions there is a kinetic equilibrium between all the body compartments. The sigmoidicity of the dose-response curve in the effect compartment for Org NC 45 ($\gamma = 5.7$) is different from that of tubocurarine ($\gamma = 2.53$) (Sheiner et al., 1979). It is possible to interpret this parameter as the mean number of molecules of the drug that act on one receptor entity to produce the effect. However, this interpretation of receptor occupancy theory does not explain all the pharmacodynamic phenomena and it is safer to consider it as one useful parameter describing the pharmacodynamic effect which can be used to make predictions with kinetic and dynamic models.

The elimination half-life for pancuronium has been found to be 110 min (Miller et al., 1978) and 127 min (Somogyi, Triggs and Shanks, 1978). The value for Org NC 45 (31 min) is much less and may explain the shorter duration of action and the more rapid rate of recovery from Org NC 45 when compared with pancuronium.

The combination of the kinetic and dynamic models described here should allow predictions to be made as to what are optimal dose regimes for use with multiple or single bolus doses and for continuous infusion regimes for Org NC 45.

ACKNOWLEDGEMENTS

This was a joint study by clinicians, analytical chemists and pharmacokineticists. To avoid an extended list of authors, only a minority is mentioned; the omitted majority is greatly acknowledged. D. Langrehr, H. Wesseling and the Department of Oral Surgery (Groningen) assisted with the clinical part; G. van der Laar, J. Paanakker and Mrs H. Wingens developed the assay; C. Timmer, G. D. de Jongh and H. P. Wijnand gave help with the pharmacokinetic modelling and preparation of the manuscript.

REFERENCES

Hull, C. J. (1979). Pharmacokinetics and pharmacodynamics. *Br. J. Anaesth.*, 51, 579.

Marshall, I. G., Agoston, S., Booij, L. H. D. J., Durant, N. N., and Foldes, F. F. (1980). Pharmacology of Org NC 45 compared with other non-depolarizing neuromuscular blocking drugs. *Br. J. Anaesth.*, 52, 11S.

Miller, R. D., Agoston, S., Booij, L. H. D. T., Kersten, U. W., Crul, J. F., and Ham, J. (1978). The comparative potency and pharmacokinetics of pancuronium and its metabolites in anaesthetized man. *J. Pharmacol. Exp. Ther.*, 207, 539.

Sheiner, L. B., Stanski, D. R., Vozeh, S., Miller, R. D., and Ham, J. (1979). Simultaneous modelling of pharmacokinetics and dynamics. Application to d-tubocurarine. *Clin. Pharmacol. Ther.*, 25, 358.

Somogyi, A. A., Triggs, E. J., and Shanks, C. A. (1978). (Abstract.) *Clin. Exp. Pharmacol. Physiol.*, 5, 250.

PHARMACOCINETIQUE ET PHARMACODYNAMIQUE D'ORG NC 45 CHEZ L'HOMME

RESUME

Une étude combinée pharmacocinétique–pharmacodynamique d'Org NC 45 a été faite sur six malades subissant une intervention oro–faciale à froid. La pharmacocinétique a pu être décrite grâce à un modèle ouvert à deux compartiments, avec une demi-vie de répartition d'environ 4 mn et une demi-vie d'élimination d'environ 31 mn. Les paramètres de la pharmacocinétique confirment les observations cliniques antérieures, à savoir qu'Org NC 45 a un début d'action plus rapide et une durée d'action plus courte que le pancuronium de même qu'un taux de récupèration plus rapide. Lorsqu'on a comparé les paramètres de pharmacocinétique et de pharmacodynamique on a pu distinguer la biophase du compartiment central et celle du compartiment périphérique. L'équilibre cinétique moyen de la concentration dans le plasma produisant un blocage de 50% de la réaction à la crispation a été de 0,137 μg ml^{-1} (plage de 0,118–0,176 μg ml^{-1}).

PHARMAKOKINESE UND PHARMAKODYNAMIK VON ORG NC 45 BEIM MENSCHEN

ZUSAMMENFASSUNG

Pharmakokinetisch–pharmakodynamische Studien von Org NC 45 wurde an 6 Patienten mit Mund/Gesichtseingriffen vorgenommen. Die pharmakokinetischen Parameter—unter Verwendung eines zeiteiligen, offenen Modells mit Verteilungshalbwertzeit von *ca.* 4 min. und Eliminierungshalbwertzeit von *ca.* 31 min—bestätigen fruhere Ergebnisse, denenzufolge Org NC 45 rascher einsetzt u. kurzer dauert als Pancuronium, mit schenellerer Erholung. Bei Vergleich der kinetischen und dynamischen Parameter konnte die Biophase aus beiden Modellteilen unterschieden werden. Die mittlere normale Plasmakonzentration fur eine 50%ige Zuckreaktion-Blockierung betrug 0,137 μg ml^{-1} (Bereich 0,118–0,176 μg ml^{-1}).

FARMACOCINETICAS Y FARMACODINAMICAS DEL ORG NC 45 EN EL HOMBRE

SUMARIO

Se efectuó un estudió farmacocinético–farmacodinámico combinado del Org NC 45 en 6 pacientes en proceso electivo de cirugía orofacial. Las farmacocinéticas pudieron describirse usando un modelo abierto de 2 compartimentos, con un periodo de media vida de distribución de aproximadamente 4 minutos y un periodo de media vida de eliminación de 31 minutos, aproximadamente. Los parámetros farmacocinéticos confirmaron los resultados clínicos anteriores de que el Org NC 45 posee una acción más rápida y de más corta duración que el pancuronium, así como un régimen de recuperación más rápido. Al comparar los parámetros farmacocinéticos y los farmacodinámicos, pudo distinguirse la biofase del compartimento central y del periférico. La concentración media y constante de plasma para producir un 50% de bloqueo de la respuesta de suspensión fue de 0,137 μg ml^{-1} (gama de 0,118–0,176 μg ml^{-1}).

Br. J. Anaesth. (1980), 52, 43S

USE OF THE HUMAN "ISOLATED ARM" PREPARATION TO INDICATE QUALITATIVE ASPECTS OF A NEW NEUROMUSCULAR BLOCKING AGENT, ORG NC 45

A. BENCINI, S. AGOSTON AND J. KET

SUMMARY

In the human isolated arm preparation Org NC 45 had a significantly faster rate of recovery and a shorter duration of action (end of injection to 90% recovery of control twitch height) than pancuronium. The isolated arm preparation is suitable for the qualitative comparison of the neuromuscular blocking activities of new and established drugs.

The isolated arm technique, more accurately described as regional neuromuscular blockade technique, was originally applied by various authors for therapeutic (Torda and Klonymus, 1966, 1967; Foldes, 1968) and diagnostic purposes (Foldes et al., 1968); it was only casually advocated as an experimental tool by these authors.

Some workers have applied this method for analysis of various aspects of neuromuscular blockade. This study was designed to determine whether the isolated arm preparation could be used as a reliable method for pilot qualitative studies of neuromuscular blocking agents. To achieve this we have compared the duration and recovery rates of a new neuromuscular blocking agent, Org NC 45, a monoquaternary analogue of pancuronium (Savage, Sleigh and Carlyle, 1980) with pancuronium, knowing from animal experiments and available clinical data that Org NC 45 is characterized by a shorter action and a quicker recovery than pancuronium (Durant et al., 1979).

MATERIALS AND METHODS

Nine healthy volunteers of both sexes were exposed at intervals of 1–2 weeks to equal doses of Org NC 45 and pancuronium in sequence. The sequence was reversed for alternate experiments. Each volunteer lay supine on an operating table with one arm secured to an armboard. A tourniquet was applied to the arm just above the epicondyles of the humerus. The same arm was used for the two experiments. An infusion of 5% glucose with a three-way stopcock was set up in the dorsum of the hand of the arm under investigation. A Gould Statham universal transducing cell UC3 with a load cell UL4-20 fixed in a handgrip preparation as described by Ali (1970) was used to sense the force of contraction of the indirectly stimulated adductor pollicis muscle which was then recorded on a Gould Brush 220 ink–paper recorder. Two steel needle electrodes inserted subcutaneously near to the ulnar nerve—one at the wrist, the other 5 cm proximal to it—applied supramaximal electrical stimuli (from a Grass S88 stimulator) of between 80 and 100 V at 0.1 Hz and 0.2 ms duration to the ulnar nerve. The last three volunteers were stimulated by percutaneous electrodes with a current of 7–10 mA at 0.2 Hz and 0.2 ms duration with a Myo-test PNS stimulator (Biometer, Copenhagen, Denmark).

A typical tracing is shown in figure 1. The tourniquet was inflated for two control periods of 5 min duration each before the injection of the drugs (not shown in the figure). In the second control period a volume of saline equal to the volume of drug solution to be injected in that person was also injected over 30 s as a control. Then, with the tourniquet inflated for 5 min, one drug in a volume of saline 0.9% that was adjusted to the size of the volunteer's forearm was injected over 30 s. Thirty minutes after recovery to control twitch height the other drug was administered. We injected both drugs on the same day to obtain as similar experimental conditions as possible.

An effort was made to obtain comparable degrees of block of 95–100% in the volunteers. The

---

A. BENCINI, M.D., F.F.A.R.C.S.; S. AGOSTON, M.D., PH.D.; J. KET, Research Group of the Institutes of Anaesthesiology and Clinical Pharmacology, State University of Groningen, Oostersingel 59, Groningen, The Netherlands.

Reprint requests to A. B.

0007-0912/80/130043-05 $01.00

© Macmillan Publishers Ltd 1980

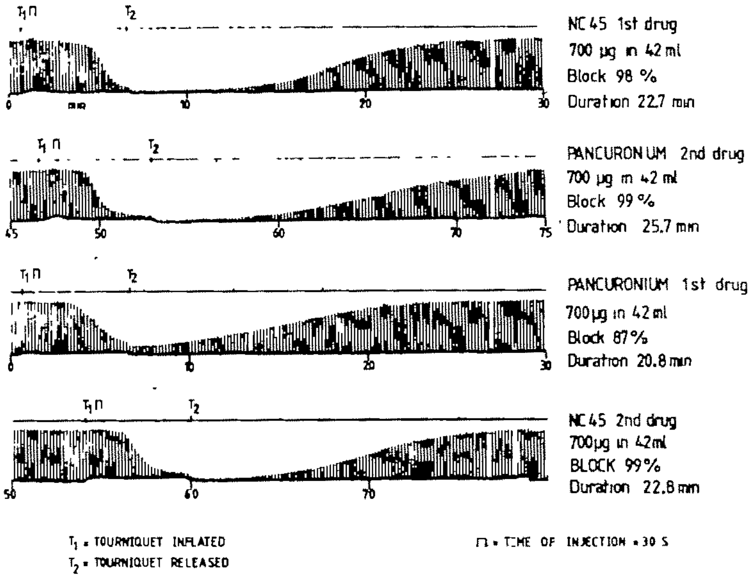


FIG. 1. A typical trace obtained in one of the experiments. Notice that pancuronium has a shorter duration of action in the third trace compared with Org NC 45 in the fourth trace because of a different maximal block.

distribution of the drug in the forearm and the dose of drug per unit forearm mass are two factors critical to the achievement of blocks of similar magnitude. The distribution of the drug solution is itself related to the volume of drug solution injected relative to the size of the forearm. The injected volume of a standard concentration of drug solution was therefore tailored to the forearm size of each volunteer by displacement of water up to a line drawn horizontally through the humeral epicondyles. We arbitrarily assigned a volume to one volunteer (30 ml in B.V., in table I), worked out empirically the equipotent doses of Org NC 45 and pancuronium required to achieve a 95% block in the isolated arm of that volunteer (500 µg each of Org NC 45 and pancuronium) and used the same concentration of drug solution for each volunteer, that is 16.66 $\mu g\ ml^{-1}$ of pancuronium and Org NC 45. This concentration produced a complete block in most of the other volunteers, so the concentration of the drug solution was in later experiments reduced to 12 $\mu g\ ml^{-1}$ and

TABLE I. *Details of experiments. Only blocks of 87–100% were analysed*

Volunteer	Volume displaced by forearm (ml)	Dose of Org NC 45 and pancuronium (µg)	Volume of Org NC 45 and pancuronium (ml)	% Block attained			
				Org NC 45 1st	Org NC 45 2nd	Pancuronium 1st	Pancuronium 2nd
B. V. (F)	1250	500	30	100	98	90	100
B. V. (F)	1250	500	30	100	—	—	100
J. K. (F)	1250	500	30	100	80	79	98
J. K. (F)	1250	400	30	—	100	100	—
S. A. (M)	1750	800	40	100	97	95	100
J. F. (M)	1750	700	40	98	97	87	100
E. N. (F)	1500	600	35	98	100	98	99
A. B. (M)	1750	400	40	99	30	10	96
T. H. (M)	2000	350	45	—	100	96	—
M. F. (M)	1750	350	40	100	96	100	100
J. M. (M)	1750	600	40	100	100	—	—

$8\ \mu g\ ml^{-1}$; but, even so, complete depression of the twitch height was obtained in most cases.

Table I shows the estimated forearm displacement volumes, the calculated injection volumes, the total doses and the percent block obtained with the drugs.

RESULTS

Recovery time from 25% to 75% of control twitch height (Recovery index)

The data were assembled into two groups. Using paired Student's *t* test we found no significant difference between recovery indices of Org NC 45 injected before and after pancuronium and those of pancuronium injected before or after Org NC 45, but there was a significant difference ($P < 0.01$) between the 25 and 75% recovery indices of Org NC 45 and pancuronium. The average (±SD) of the recovery indices was 7.90±3.41 min ($n = 18$) for Org NC 45 and 12.15±5.14 min ($n = 16$) for pancuronium. Thus the recovery index of Org NC 45 is approximately 35% less than that of pancuronium.

TABLE II. *Comparison of recovery index of Org NC 45 and pancuronium in the isolated arm. *Injected 20 min after recovery from same dose of pancuronium; †injected 20 min after recovery from same dose of Org NC 45. Differences between drugs statistically significant ($P < 0.01$)*

	Org NC 45 (min)	Pancuronium (min)
	4.6	22.1
	5.3	9.9
	10.6	8.9
	7.8	12.8
	6.2	14.0
	7.2	13.8
	6.7	24.0
	5.1	2.4
	12.6	7.2†
	12.0	11.0†
	5.8*	13.2†
	5.0*	12.4†
	8.8*	14.7†
	9.8*	8.4†
	5.8*	7.8†
	6.2*	11.8†
	15.0*	
	12.1*	
Mean	7.90	12.15
SD	3.41	5.14
n	18	16

Duration of block from end of injection to 90% recovery

The same statistical analysis was applied to compare the duration of block from the end of injection to 90% recovery of twitch height (table III. The overall mean±SD of Org NC 45 was 25.75±9.25 min ($n = 17$) when compared with pancuronium (33.93±12.13 min ($n = 16$)), which makes Org NC 45 of 24% shorter duration. This difference is statistically significant at the 5% level ($P < 0.05$).

TABLE III. *Comparison of the time from end of injection to 90% recovery of control twitch tension following injection of Org NC 45 and pancuronium to the isolated arm. *Org NC 45 administered 20 min after recovery from pancuronium, †pancuronium administered 20 min after recovery from Org NC 45. Difference between drugs statistically significant ($P < 0.05$)*

	Org NC 45 (min)	Pancuronium (min)
	16.5	56
	32.0	33.2
	32.2	22.9
	18.8	37.1
	24.7	41.4
	46.2	37.6
	23.2	38.0
	22.7	20.8
	35.4	22.4†
	31.8*	27.2†
	19.0*	40.0†
	25.96*	32.6†
	29.5*	64.1†
	32.1*	22.2†
	22.8*	25.7†
	25.0*	21.8†
	26.4*	
Mean	25.75	33.93
SD	9.25	12.13
n	17	16

DISCUSSION AND CONCLUSION

Although both indices of neuromuscular blocking activity for the two drugs were significantly different and parallel to the directions expected from clinical and animal experiments, the recovery index shows less variability than the duration from end of injection to 90% recovery of control twitch time. Only in one of 18 experiments (5.5%) was the recovery index of Org NC 45 longer than that of pancuronium, as opposed to four of 18 experiments (22.2%) for the index of duration. In all of the last four cases the complete neuromuscular block attained with Org NC 45 was longer by several minutes than that of pancuronium.

The need to compare blocks of similar magnitude and similar duration of complete blocks is apparent. In this study we have compared blocks of between 87 and 100%; others were discarded. The 100% neuromuscular blocks themselves were of different duration and ranged from 1.5 to 12.5 min (table IV).

TABLE IV. *Per cent block obtained and duration of maximal block (min, in parentheses)*

	Org NC 45 1st	Org NC 45 2nd	Pancuronium 1st	pancuronium 2nd
B. V.	100 (5.5)	98 (3)	90 (3 5)	100 (16)
B. V.	100 (1.4)	—	—	100 (3)
J. K.	100 (3)	80 (1.5)	79 (2)	98 (1)
J. K.	—	100 (6)	100 (8.76)	—
S. A.	100 (5)	97 (2)	95 (2.5)	100 (3.5)
J. F	98 (1)	97 (3)	87 (1.5)	100 (2)
E. N.	98 (4)	100 (3)	98 (4)	99 (2)
A. B.	99 (3)	30 (1)	10 (1)	96 (3.5)
T. H.	—	100 (3.44)	96 (1)	—
J. M.	100 (8.5)	—	—	100 (3.5)
M. F.	100 (6)	96 (6)	100 (2.36)	100 (1.32)

If only blocks of, say, 98–100% and of similar duration were compared, then few experiments would be needed and the method would be more useful.

It is difficult to achieve blocks of comparable magnitude with a few experiments, however. The equipotent doses of Org NC 45 and pancuronium in the isolated arm have first to be determined. Even then the dose required to achieve a predetermined block shows both between- and within-person variation. Several factors probably combine to give this variability; these include controllable technical factors, such as fixation of the arm and proper placement of needle electrodes, and relatively uncontrollable factors such as the volunteer's mental and physical state and the distribution of the drug solution in the forearm vasculature. The physical and physicochemical disturbances produced by pressure in the forearm and ischaemia when the cuff is inflated have been neither elucidated nor controlled. However, several workers (Botelho and Cander, 1953; Torda and Klonymus, 1966; Foldes et al., 1968) have pointed out that neuromuscular transmission is not depressed measurably by 15 min of ischaemia. In this study we saw no depression of twitch height after 5 min of cuff inflation. Sometimes the twitch height increased by 10–15% (as noted by Horst-Larsen, 1976), but came back to normal after release of the cuff.

If the duration parameter is very dependent on the degree of block obtained, the recovery index seems to be less affected by such variations. The mechanisms of recovery from neuromuscular blockade are less susceptible than the development phase to erratic experimental processes, some of which have been mentioned above. The reliability of this index in this study is supported by our clinical results (Agoston et al., 1980) in which the recovery index of Org NC 45 in anaesthetized patients was similar to that obtained in this study. In their isolated arm experiments Agoston, Feldman and Miller (1979) also obtained an estimate for pancuronium comparable to ours (10±2 min *v.* 12±5 min respectively). Were similar reliable indices for duration of action to be developed, then again the method would be more powerful.

To conclude, the isolated arm lends itself to comparative qualitative evaluation of the neuromuscular blocking activities of neuromuscular blocking drugs. Some indices, such as the recovery indices, are more constant in spite of variable magnitude and duration of blocks and need fewer experiments for comparative assessment.

ACKNOWLEDGEMENTS

Special thanks to Sr B. Velthuis for her all-round co-operation as well as volunteering for several experiments. We express our gratitude to the volunteers who were, apart from Sr Velthuis and the authors: Ton Hilkemeijer, Hans Wesenhagen, Mohammed Fouad, Jeroen Mass, Jan Fens and Elselien Noordijk.

REFERENCES

Agoston, S., Feldman, S. A., and Miller, R. D. (1979). Plasma concentrations of pancuronium and neuromuscular blockade after injection into the isolated arm, bolus injection and continuous infusion. *Anesthesiology*, **51**, 119.

—— Salt, P., Newton, D., Bencini, A., Boomsma, P., and Erdmann, W. (1980). The neuromuscular blocking action of Org NC 45, a new pancuronium derivative in anaesthetized patients. A pilot study. *Br. J. Anaesth.*, **52**, 53S.

Ali, H. H. (1970). A new device for monitoring force of thumb adduction. *Br. J. Anaesth.*, **42**, 83.

Botelho, S. Y., and Cander, L. (1953). Post-tetanic potentiation before and during ischemia in intact human skeletal muscle. *J. Appl. Physiol.*, **6**, 221.

Durant, N. N., Marshall, I. G., Savage, D. S., Nelson, D. J, Sleigh, T., and Carlyle, I. C. (1979). The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45 and other pancuronium analogues, in the cat. *J. Pharm. Pharmacol.*, **31**, 831.

Foldes, F. F. (1968). Regional intravenous neuromuscular block: a new diagnostic and experimental tool. *Proc. 4th World Congr. Anaesthesiol.*, London, p. 425.

—— Klonymus, D. H., Maisel, W., and Osserman, K. E. (1968). A new curare test for the diagnosis of myasthenia gravis. *J.A.M.A.*, **203**, 649.

Horst-Larsen, H. (1976). The hydrolysis of suxamethonium in human blood. *Br. J. Anaesth.*, **48**, 887.

Savage, D. S., Sleigh, T., and Carlyle, I. C. (1980). The emergence of Org NC 45, 1-[(2β-3α,5α,16β,17β)-3,17-bis-(acetyloxy)-2-(piperidinyl)-androstan-16-yl]-1-methyl-piperidinium bromide, from the pancuronium series. *Br. J. Anaesth.*, **52**, 3S.

Torda, T. A. G., and Klonymus, D. H. (1966). Regional neuromuscular block. *Acta Anaesthesiol. Scand.* (Suppl. 24), 177.

—— —— (1967). The regional use of muscle relaxants. *Arch. Surg.*, **94**, 199.

UTILISATION D'UNE PREPARATION DE BRAS HUMAIN ISOLE POUR INDIQUER LES ASPECTS QUALITATIFS D'UN NOUVEL AGENT DE BLOCAGE NEUROMUSCULAIRE: ORG NC 45

RESUME

Dans une préparation de bras humain isolé, on a obtenu avec Org NC 45 un taux de récupération nettement plus rapide et une durée d'action plus courte qu'avec le pancuronium (de la fin de l'injection à 90% de récupération de la hauteur de la crispation témoin). La préparation de bras isolé convient pour la comparaison qualitative du blocage neuromusculaire des médicaments nouveaux et de ceux ayant déjà fait leurs preuves

VERWENDUNG DES MENSCHLICHEN "ISOLIERTEN ARM-PRÄPARATES" ZUR FESTSTELLUNG DER QUALITATIVEN ASPEKTE EINES NEUEN NEUROMUSKULÄREN BLOCKIERUNGSMITTELS, ORG NC 45

ZUSAMMENFASSUNG

In dem menschichen isoliertem Arm-Praparat zeigte Org NC 45 ein wesentlich rascheres Erholungstempo und eine kürzere Wirkungsdauer (Injektionsende bis zu 90%igem Erreichen der Kontroll-Zuckhohe) als Pancuronium. Das isolierte Armpräparat ist geeignet für den qualitativen Vergleich der neuromuskularen Blockierungsaktivitat bei neuen und etablierten Drogen.

PREPARACION DEL "BRAZO AISLADO" PARA INDICAR LOS ASPECTOS CUALITATIVOS DE UN NUEVO AGENTE DE BLOQUEO NEUROMUSCULAR, EL ORG NC 45

SUMARIO

El Org NC 45 mostró, en la preparación del "brazo aislado", un régimen de recuperación significativamente más rápido y una acción de más corta duración que el pancuronium (desde el término de la inyección hasta una recuperación del 90% de la altura del control de sustención). La preparación del "brazo aislado" es adecuada para la comparación cualitativa de las actividades de bloqueo neuromuscular a llevar a cabo entre las nuevas drogas y las ya establecidas.

Br. J. Anaesth. (1980), 52, 49S

FIRST CLINICAL EXPERIENCES WITH ORG NC 45

J. F. CRUL AND L. H. D. J. BOOIJ

SUMMARY

The new short-acting steroid muscle relaxant Org NC 45 was tested clinically in 18 patients and compared with a similar application of pancuronium bromide in 22 patients. Onset, duration and slope of recovery were significantly shorter for Org NC 45. No cumulative effects were noticed over several consecutive doses of Org NC 45. No tachycardia or arterial pressure changes were noticed with doses of Org NC 45 up to 130 μg kg^{-1}, which was three times the 95% blocking dose.

In the search for a short-acting, non-depolarizing neuromuscular blocking drug devoid of cardiovascular side-effects, animal experiments indicated that the monoquaternary homologue of pancuronium, Org NC 45 (3α, 17β-diacetoxy-2β, 16β-dipiperidino-5α androstane 16β-N monomethobromide), might fulfil these criteria (Buckett, Hewett and Savage, 1973; Durant et al., 1979; Savage, Sleigh and Carlyle, 1980). After *in vivo* and *in vitro* experiments in animals (Marshall et al., 1980) we started our first clinical trials in 1977, to assess the potency of Org NC 45 and its time-course of action in comparison with pancuronium, and to study the possible cardiovascular effects. This paper reports the findings of this study. A more detailed comparison with other neuromuscular blocking drugs is reported elsewhere (Krieg, Crul and Booij, 1980).

METHODS

Forty adult patients of ASA status I or II undergoing abdominal or limb surgery gave informed consent to the study. Each was given as premedication nicomorphine 7.5–10 mg i.m., droperidol 2.5 mg i.m. and atropine 0.25 mg. Anaesthesia was induced with thiopentone 4 mg kg^{-1} i.v. and fentanyl 1.5 μg kg^{-1} i.v. and maintained by nitrous oxide 6 litre min^{-1} and oxygen 3 litre min^{-1} by mask. The larynx and trachea were sprayed with 4% lignocaine and the trachea was intubated. Additional doses of fentanyl 50μg or droperidol 2.5 mg, or both, were given if needed.

The right ulnar nerve was stimulated via subcutaneous needles at the wrist using pulses of supramaximal intensity and of 0.2 ms duration at a rate of 0.1 Hz, generated by a Grass S48 stimulator. The force generated by the adductor pollicis was recorded using a Statham UC3 force displacement transducer. The compound electromyogram (e.m.g.) of the hypothenar muscles was recorded using the methods described by Lee and his colleagues (1977). Both records were displayed using a Brush recorder.

E.c.g. and a finger plethysmogram were also recorded continuously, together with the heart rate derived from one of these two signals. Arterial pressure was recorded indirectly every 5 min during anaesthesia and at 2-min intervals after giving any neuromuscular blocking drug.

The patients were divided into two groups, 18 receiving Org NC 45 and 22 pancuronium. Each patient was given either single or multiple doses of either drug to produce sufficient relaxation for the surgery and to allow us to determine the dose-response curves for the two drugs. In five of the patients given Org NC 45 cumulative small doses were given to allow an assessment of the dose blocking 95% of the twitch response. In this group multiple sub-paralytic doses of Org NC 45 were given when the twitch height and e.m.g. had returned to their control values, to assess any possible cumulative action. Having determined the 95% blocking dose from these five patients, we used this value in other patients to compare the onset, duration and recovery rate of Org NC 45 and pancuronium. The time of onset (from the end of the injection to the maximal effect), the duration of effect (from the end of injection to 90% recovery) and the recovery index (the time from 25%

J. F. CRUL, M.D., PH.D., F.F.A.R.C.S.; L. H. D. J. BOOIJ, M.D.; Department of Anesthesiology, University Hospital, Geert Groote Plein Zuid 12, Nijmegen, The Netherlands.

0007–0912/80/130049–04 $01.00

© Macmillan Publishers Ltd 1980

to 75% recovery) were measured, if possible, after each administration of the neuromuscular blocker.

In four patients given Org NC 45, when recovery to 20% of the twitch had occurred, pyridostigmine 0.13 mg kg^{-1} was given i.v. and the time to 95% recovery measured.

We looked carefully for any signs of histamine release or bronchospasm.

RESULTS

The maximum depression of twitch produced by Org NC 45 and pancuronium for the doses used are shown in figure 1, with the lines of best fit calculated by a least-squares method. There were no differences between the lines for the first and subsequent doses of Org NC 45. The line for Org NC 45 is to the left of that for pancuronium, showing it to be more potent. The doses needed to produce a 50% block (ED_{50}) were Org NC 45 28 µg kg^{-1} and pancuronium 42 µg kg^{-1}. The slopes of the curves did not differ significantly.

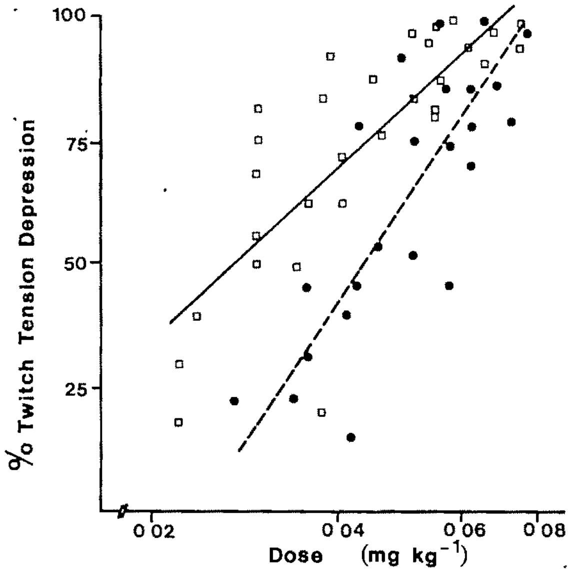


FIG. 1. Dose-response relationship of single and cumulative doses of Org NC 45 (□——□) and pancuronium bromide (●- - -●) in man ($n = 18$ for Org NC 45, 22 for pancuronium).

The onset times, durations and recovery indices for both drugs given in 95% blocking doses are shown in figure 2. All these were significantly greater for pancuronium.

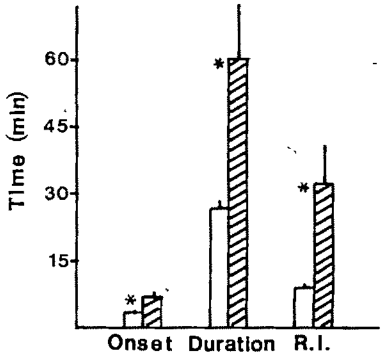


FIG. 2. Onset, duration and slope of recovery (R.I.) of a 95% neuromuscular blocking dose of Org NC 45 0.043 mg kg^{-1} and pancuronium 0.065 mg kg^{-1} in man ($n = 18$ for Org NC 45, 22 for pancuronium). *Significant difference at the $P < 0.05$ level.

The duration of clinical relaxation (the time from injection to recovery of 25% of the twitch force) from a dose just producing full paralysis was 15 min for Org NC 45 and 32 min for pancuronium. When used in up to four or five subparalytic doses, the degree of paralysis and the recovery index with each dose of Org NC 45 did not change (fig. 3). In contrast, repeated doses of

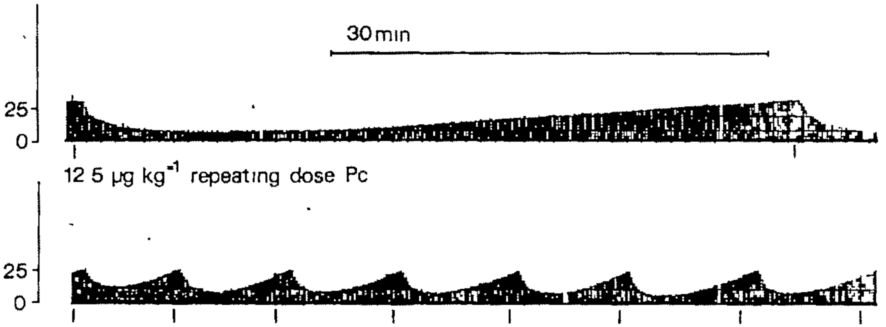


FIG. 3. Time-course of action of first and maintenance doses of pancuronium and Org NC 45 on the ulnar nerve/adductor pollicis muscle in man Doses chosen closely imitate the way in which muscle relaxation is maintained in man.

pancuronium led to a more intense block and a prolonged duration of effect.

The time-courses of the e.m.g. responses were similar to those of the twitch response. No changes in arterial pressure or heart rate occurred after giving Org NC 45 even in doses of up to three times the 95% blocking dose, whereas some degree of tachycardia and an increase in arterial pressure were usually seen after giving pancuronium. There were no signs of bronchospasm or histamine release with Org NC 45.

In the four patients given pyridostigmine, recovery of neuromuscular transmission was prompt and complete (95% recovery) within 5 min.

DISCUSSION

Org NC 45 proved to be a neuromuscular blocking drug slightly more potent than pancuronium, but with a considerably shorter duration of action and faster recovery time. In addition, the time of onset was shorter, although not dramatically so (fig. 2). An absolute comparison of the dose–response curves could not be performed because the dose–response relationships were not measured for drugs in the same patients.

The lack of cumulative effect of Org NC 45 could not be compared fully with pancuronium in this study, and it needs other more accurate studies set up especially for this purpose. Norman, Katz and Seed (1970) showed a cumulative effect for pancuronium. After a full paralysing dose of Org NC 45, clinical relaxation (blocks of more than 50%) lasted for about 15 min. This should enable most short operative procedures to be performed using Org NC 45 alone, without the need for suxamethonium or an antagonizing agent. For longer operations the administration of a continuous infusion technique will be possible.

The absence of side-effects of Org NC 45 on heart rate and arterial pressure as well as on the electrocardiogram was noteworthy, in comparison with the almost obligatory occurrence of tachycardia with pancuronium. The absence of stimuli by intubation or surgical intervention during the recording of these parameters made the observation more striking. The absence of signs of bronchoconstriction or histamine release does not necessarily imply that they will not occur in patients particularly sensitive to histamine release, or those having other allergic conditions.

REFERENCES

Buckett, W. R., Hewett, C. L., and Savage, D. S (1973). Pancuronium bromide and other steroidal neuromuscular blocking agents containing acetylcholine fragments *J Med. Chem.*, **16**, 1116.

Durant, N N., Marshall, I. G., Savage, D. S., Nelson, D. J., Sleigh, T., and Carlyle, I. C. (1979). The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45, and other pancuronium analogues, in the cat. *J. Pharm. Pharmacol.*, **31**, 831.

Krieg, N., Crul, J. F., and Booij, L. H. D. J. (1980). The relative potency of Org NC 45, pancuronium alcuronium and tubocurarine in anaesthetized man. *Br. J. Anaesth.*, **52**, 783.

Lee, C., Katz, R. L., Lee, A. S. J., and Glaser, B (1977). A new instrument for continuous recording of the evoked compound electoromyogram in the clinical setting. *Anesth. Analg. (Cleve.)*, **56**, 260.

Marshall, I. G., Agoston, S., Booij, L. H. D. J., Durant, N N., and Foldes, F. F. (1980). Pharmacology of Org NC 45 compared with other non-depolarizing neuromuscular blocking drugs. *Br. J. Anaesth.*, **52**, 11S.

Norman, J., Katz, R. L., and Seed, R. F. (1970). The neuromuscular blocking action of pancuronium in man during anaesthesia. *Br. J. Anaesth.*, **42**, 702.

Savage, D. S., Sleigh, T., and Carlyle, I. C. (1980). The emergence of Org NC 45, 1-[(2β, 3α, 5α, 16β, 17β)-3,17-bis(acetyloxy) - 2 - (1 - piperidinyl) - androstan - 16 - yl] - 1 - methylpiperidinium bromide, from the pancuronium series. *Br. J. Anaesth.*, **52**, 3S.

PREMIERES EXPERIENCES CLINIQUES AVEC ORG NC 45

RESUME

Le nouveau décontracturant musculaire à courte durée d'action: Org NC 45, a été soumis à des essais cliniques sur 18 patients et comparé à des applications similaires de bromure de pancuronium sur 22 patients. Le commencement de l'action, sa durée et le coefficient de récupération ont été nettement plus courts dans le cas d'Org NC 45. On n'a remarqué aucun effet cumulatif lorsque l'on a utilisé plusieurs doses consécutives d'Org NC 45. Il n'a été remarqué ni tachycardie, ni variations dans la pression artérielle, avec des doses d'Org NC 45 allant jusqu'à 130 µg kg^{-1}, ce qui était équivalent à trois fois la dose nécessaire pour obtenir un blocage à 95%.

ERSTE KLINISCHE ERFAHRUNGEN MIT ORG NC 45

ZUSAMMENFASSUNG

Das neue, kurzwirkende Steroid-Muskelentspannungsmittel Org NC 45 wurde klinisch an 18 Patienten getestet und mit einer ähnlichen Anwendung von Pancuroniumbromid an 22 Patienten verglichen. Einsatz, Dauer und Erholungskurve waren für Org NC 45 wesentlich kürzer, und auch nach widerholten aufeinanderfolgenden Dosen von Org NC 45 kam es zu keiner Kumulation. Weder Tachykardie noch Änderungen des arteriellen Druckes wurden bei Dosen von Org NC 45 bis zu 130 µg kg^{-1} festgestellt, also bei einer 3 mal höheren Dosis als der, die eine 95%ige Blockierung bewirkt.

PRIMERAS EXPERIENCIAS CLINICAS CON EL ORG NC 45

SUMARIO

El nuevo relajante muscular, esteroide y de corta duración, el Org NC 45, se verificó clínicamente en 18 paciente y se comparó con une aplicación similar de bromuro de pancuronium en 22 pacientes. La acción, duración y la pendiente de recuperación fueron significativamente más cortas para el Org NC 45. Nc se apreciaron efectos acumulativos después de varias dosis consecutivas de Org NC 45. No se pareciaron taquicardia ni cambios en la presión arterial con dosis de hasta 130 μg kg^{-1} de Org NC 45, lo que representa el triple del 95% de la dosis de bloqueo.

Br. J. Anaesth. (1980), **52**, 53S

THE NEUROMUSCULAR BLOCKING ACTION OF ORG NC 45, A NEW PANCURONIUM DERIVATIVE, IN ANAESTHETIZED PATIENTS

A pilot study

S. AGOSTON, P. SALT, D. NEWTON, A. BENCINI, P. BOOMSMA AND W. ERDMANN

SUMMARY

The neuromuscular blocking effects of the new monoquaternary analogue of pancuronium, Org NC 45, have been investigated in anaesthetized patients. In different doses administered as a single i.v. bolus or as an initial bolus followed by several small maintenance doses or by a continuous infusion, Org NC 45 appears to be approximately as potent as pancuronium, but has a more rapid onset of action, considerably shorter duration of action and faster recovery rate than pancuronium. It showed no cumulative effects even after 10 maintenance doses were injected in succession. Doses of 0.08 mg kg^{-1} provided ideal intubating conditions in 90–95 s. Infusions of Org NC 45 provided much smoother control of neuromuscular blockade than did pancuronium. No cardiovascular side-effects were noted even at the greatest dose (0.12 mg kg^{-1}) used. Org NC 45 has clear advantages over pancuronium and represents a potentially valuable addition to the armamentarium of clinically useful muscle relaxants

Some 10 years ago at similar meetings, the preliminary results obtained with a new non-depolarizing muscle relaxant, pancuronium bromide, were reported. Most of the clinical reports on pancuronium at that time emphasized the safe antagonism of its action and the remarkable absence of side-effects such as histamine release and cardiovascular changes. Reports on the relative absence of side-effects of pancuronium encouraged the use of large doses of this compound instead of suxamethonium for tracheal intubation. They led to an increasing number of reports on side-effects, particularly those affecting the cardiovascular system. Accumulated clinical experience and more careful studies during the past few years focused attention on the cardiovascular side-effects of the neuromuscular blocking agents in general and those of pancuronium in particular. This, and the need for a non-depolarizing muscle relaxant with rapid onset time and short duration of action, stimulated the search for a shorter acting drug which would interact more selectively with the receptors at the neuromuscular junction, leaving other cholinergic sites unaffected at least after full paralysing doses. From early animal experiments (Durant et al., 1979) with pancuronium derivatives, Org NC 45 emerged as the most promising. We report here observations on the neuromuscular blocking action of Org NC 45 in patients undergoing anaesthesia. We have investigated the potency, the onset time, duration of action and recovery time of various doses of Org NC 45, administered as a single i.v. bolus, as an initial bolus followed by several small maintenance doses or by a continuous infusion during long-lasting operations.

METHODS

All patients were premedicated with atropine 0.5 mg i.m., and diazepam 10 mg orally. In a few patients papaveretum 10 mg i.m. instead of diazepam was given, approximately 1 h before induction of anaesthesia. Anaesthesia was induced with thiopentone 200–300 mg and fentanyl 1.5 µg kg^{-1} i.v. Intubation was facilitated either with Org NC 45 0.07, 0.1 or 0.12 mg kg^{-1}, or with suxamethonium 1 mg kg^{-1}. Anaesthesia was maintained with a gas mixture of nitrous oxide 6 litre min^{-1} and oxygen 3 litre min^{-1} and repeated small doses of fentanyl and droperidol.

Before induction of anaesthesia the right forearm and hand of the patient were secured firmly to an armboard and a force displacement transducer (Statham UC 3) was attached to the patient's hand. The ulnar nerve was stimulated at

---

S. AGOSTON, M.D., PH.D.; P. SALT, M.A., M.B., B.CHIR., PH.D.; D. NEWTON, M.B.B.S., F.F.A.R.C.S.; A. BENCINI, M.D., F.F.A.R.C.S., P. BOOMSMA, M.D.; W. ERDMANN, M.D., PH.D.; Research Group of the Institutes of Anaesthesiology and Clinical Pharmacology, State University of Groningen, Oostersingel 59, Groningen, The Netherlands.

Reprint requests to S. A.

0007-0912/80/130053-07 $01.00

© Macmillan Publishers Ltd 1980

the wrist by needle electrodes with square-wave, supramaximal stimuli of 0.2 ms duration at the rate of 0.1 Hz. The isometric twitch tension of the indirectly stimulated adductor pollicis muscle was recorded on a Brush Clevite or Siemens ECG recorder. After the control twitch tension became constant (usually in 6–10 min) the patients received i.v. either suxamethonium or Org NC 45 for endotracheal intubation. In those patients who received suxamethonium, the selected dose of Org NC 45 was administered after full recovery of suxamethonium effects.

The e.c.g. was monitored throughout the investigation. Continuous e.c.g. recordings were obtained during 2 min before and 5 min after the administration of Org NC 45 and examined for evidence of chronotropic side-effects. Arterial pressure was recorded indirectly by sphygmomanometer and inflatable arm cuff every 2 min after injection of each dose of Org NC 45 for 10 min or every 5 min during Org NC 45 infusions.

In assessing the neuromuscular effects of Org NC 45 we measured *onset time* (the time from the end of injection until maximum effect was reached), *duration* (the time between the end of the injection until recovery of the twitch height to 90% of control) and *recovery time* (the time required from 25% to 75% recovery of the twitch force.

Three types of experimental programme were followed:

Short-lasting operations

A. single bolus injection of Org NC 45 0.03 mg kg^{-1}, 0.05 mg kg^{-1}, 0.07 mg kg^{-1}, 0.1 mg kg^{-1} or 0.12 mg kg^{-1} was given into a fast running infusion. At 90 s following the injection of the bolus of Org NC 45, intubation was attempted and the conditions noted.

Long-lasting operations with multiple bolus injections of Org NC 45

Bolus injection of Org NC 45 0.07 mg kg^{-1}, 0.08 mg kg^{-1} or 0.1 mg kg^{-1} were followed by small maintenance doses (1/5 of the initial dose) in succession whenever the twitch height returned to 25% of control. The time between maintenance doses, and the recovery time (25–75% recovery time) after the last maintenance dose were noted.

Long-lasting operations; infusion of Org NC 45

In these investigations the trachea of all patients was intubated following suxamethonium. Several minutes after the twitch height returned to control values a bolus injection of Org NC 45 sufficient to give a 70–90% block was given. When the maximum twitch height depression was obtained an i.v. infusion of Org NC 45 0.05 mg ml^{-1} in saline was started and maintained to give a constant 90% depression of the adductor pollicis twitch response. When a steady 90% block had been maintained with a constant infusion rate of Org NC 45 for at least 30 min, this infusion rate was noted and the infusion then stopped. Twitch height was allowed to return to 100% of control and the recovery time was again measured. In order to provide some comparison between Org NC 45 and pancuronium, similar infusion studies were performed with pancuronium in a small number of patients.

RESULTS

The onset time of Org NC 45 was rapid and appeared to be dose-dependent (tables I and II). Following the administration of Org NC 45 (30, 50, 70, 80, 100 or 120 µg kg^{-1}) the maximal effect developed in about 2–5 min.

After injection of a dose of 0.07 mg kg^{-1} intubation was possible in all patients in 90–95 s. At these times the adductor pollicis twitch height was always more than 50% of the control (fig. 1).

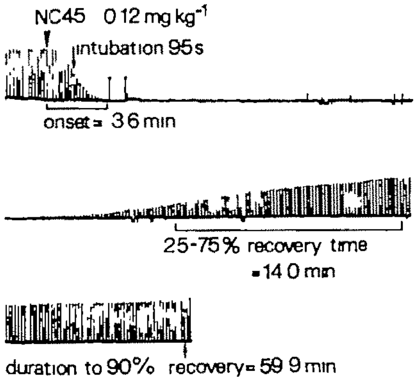


FIG. 1. Onset time, duration of action and recovery time following the administration of Org NC 45 0.12 mg kg^{-1}. Intubating conditions were excellent during a partial block.

The intubating conditions were ideal with doses of 0.08 mg kg^{-1} or greater, with complete vocal cord relaxation at 90–100 s and no bucking on the tube. With the 0.07 mg kg^{-1} dose, three out of the nine patients (tables I and II) had incomplete cord relaxation and experienced bucking on the tube. In

B.J.A. 5

BRITISH JOURNAL OF ANAESTHESIA

IF THE MAILING ADDRESS SHOWN ON THE ADDRESS LABEL NEEDS AMENDING IN ANY WAY THEN PLEASE INDICATE THE CORRECT ADDRESS HERE AND RETURN THIS COMPLETE SHEET TO:-

Circulation Department, Macmillan Journals Ltd.,
Brunel Road, Basingstoke, Hampshire RG21 2XS (England)

Full and correct address to which copies should be sent →

IMPRIME PERMIS NUMERO RT

0000 S 001 MIN7160 AN
LIBRARY
CALCUTTA UNIV COLLEGE OF MED
GOENKA HOSPITAL
145 MUKTARAM BABU STREET
CALCUTTA 700 007
WEST BENGAL
INDIA

If undelivered return to
MACMILLAN JOURNALS LTD
British Journal of Anaesthesia
(ISSN 0007–0912)
c/o Mercury Airfreight International Ltd
PO Box 83
Rotterdam 3000AB
HOLLAND

PORT PAYÉ
ROTTERDAM

TABLE I. *The neuromuscular effects of variable single doses of Org NC 45 in man (mean ± SEM; range in parentheses). *n = 6; †n = 4; §n = 4; ‡n = 7. Because of inadequate relaxation, additional doses were given before spontaneous recovery to 75% (†) and 90% (*) could be obtained in six and four patients respectively. Early termination of operation necessitated the administration of a reversal agent before recovery to 90% of control in one patient in each group (§‡)*

Dose (mg kg^{-1})	n	Percent block	Onset time (min)	Duration (min)	Recovery rate (min)
0.03	10	73.0±5.1 (48–100)	5.0±0.4 (2.4–7.8)	14.7±1.1* (11.6–18.8)	9.1±1.9† (4.8–13.7)
0.05	6	97.6±1.6 (90–100)	4.5±0.6 (2.4–6.5)	26.8±3.5§ (19.3–33.4)	9.0±0.7 (6.0–11.1)
0.07	5	99.8±0.2 (99–100)	4.3±0.6 (3.1–7.0)	37.0±5.9 (24.5–59.5)	9.0±1.1 (5.5–12)
0.10	8	100	2.4±0.2 (1.4–3.3)	44.1±3.9‡ (33–62)	11.6±1.1 (6.0–15.2)
0.12	6	100	2.7±0.5 (1.5–4.6)	60.2±4.0 (41.5–76)	15.5±1.5 (11.5–22.4)

TABLE II. *Org NC 45 in long-lasting operations; duration to 25% recovery of repeated bolus injection (mean ± SEM; range in parentheses)*

Initial dose					Maintenance doses			
mg kg^{-1}	n	Block (%)	Onset (min)	Duration to 25% recovery (min)	mg kg^{-1}	n	Duration to 25% recovery (min)	25–75% Recovery time after last injection (min)
0.07	4	93.5±2.5 (85–99)	4.7±0.8 (3–6.9)	17.8±4.6 (10–31.1)	0.014	15	7.4±1.5 (2.3–16.5)	11.0±3.9 (3.8–21.8)
0.08	3	100	3.9±1.1 (2–5.8)	27.9±2.5 (24.8–33.0)	0.016	13	14.0±1.7 (8.6–19.0)	Reversal agent used
0.1	3	100	2.2±0.5 (1.1–3.0)	26.5±8.8 (11.1–41.1)	0.02	12	18.8±5.2 (9.0–33.8)	17.0±4.1 (11–24.8)

all other patients receiving Org NC 45 less than 0.07 mg kg^{-1}, suxamethonium was used for intubation.

The duration with a single bolus injection of Org NC 45 was clearly related to the dose (table I) ranging from 14.7±1.1 min (mean ± SEM; $n = 6$) at 0.03 mg kg^{-1} to 60.2±4.0 min (mean ± SEM; $n = 6$) at 0.12 mg kg^{-1} (fig. 1, table I).

In this study we used pancuronium 0.1 mg kg^{-1} in two patients only. The duration of the blocks in these two patients were 150 and 170 min respectively.

In the long-lasting operations in which repeated doses were given following an initial single bolus injection, there was little or no evidence for accumulation (fig. 2), regardless of the number of the maintenance doses, which varied from three to 12 depending on the duration of the operation.

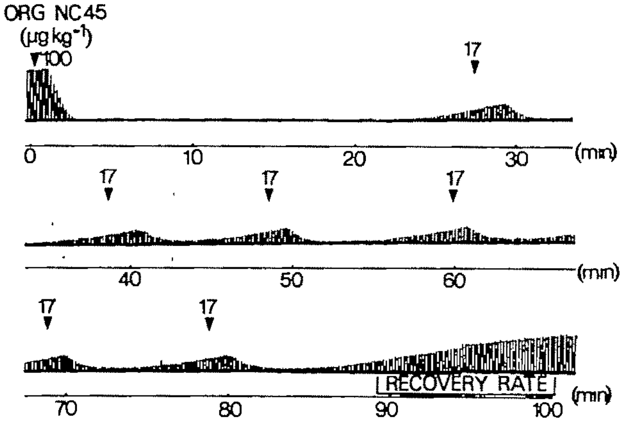


FIG. 2. The neuromuscular blocking effect of repeated doses of Org NC 45 in man. Note the regularity of the time intervals between the maintenance doses.

TABLE III. *Infusions with Org NC 45 (mean ± SEM)*

Patient	Constant infusion rate for 90% block ($\mu g\ kg^{-1}\ h^{-1}$)	Total dose (mg)	Duration of infusion (min)	25–75% Recovery time (min)	
1	76	12.6	135	10.5	14.5 ± 1.5
2	65	4.9	57	17.8	
3	70	4.0	52	12.5	
4	53	5.5	36	10.1	
5	35	7.0	110	8.6	
6	11	4.3	120	14.0	
7	11	2.5	36	16.5	
8	85	23.9	124	18.3	
9	87	25.0	202.5	22.0	

The duration of 25% recovery following the initial dose ranged from 17.8 ± 4.6 min (mean ± SEM; $n = 4$) at 0.07 mg kg^{-1} to 26.5 ± 8.8 min (mean ± SEM; $n = 3$) at 0.1 mg kg^{-1} (table II).

The time between maintenance doses was dependent on the size of the maintenance dose. When all data within each of the three dose groups was pooled, the time intervals between the maintenance doses ranged from a mean time of 7.4 ± 1.5 min (mean ± SEM; $n = 15$) at 0.014 mg kg^{-1} to 18.8 min (mean ± SEM; $n = 12$) at 0.02 mg kg^{-1} (table II).

It was found that it was possible to obtain a constant 90% block by means of an infusion of Org NC 45 for long periods of time (36–202 min) without altering the infusion rate once the desired level of block had been achieved (table III). However, the infusion rate required for the maintanance of the 90% block varied widely between patients, ranging from 11 μg kg^{-1} h^{-1} to 87 μg kg^{-1} h^{-1} (table III). Furthermore, the required infusion rate for the maintenance of a steady 90% twitch height depression was more readily obtained with Org NC 45 than with pancuronium, with a more prompt response to changes in infusion rate. Fluctuations in the level of block were less than normally experienced with pancuronium infusions.

The most striking finding in this study is provided by the 25–75% recovery times. Following single injections, multiple injections or long-lasting infusions, regardless of the dose of Org NC 45, the recovery times were remarkably short and relatively constant with mean values ranging between 9 and 17 min (tables I, II, III). The recovery times following single bolus injections, multiple injections or after prolonged infusions are summarized in tables I, II and III.

DISCUSSION

Comparative data on the speed of onset, duration of action and recovery rate of neuromuscular blocking drugs can only be viewed in relation to the size of the dose, provided that the compounds compared are administered in equipotent doses. Because of the lack of comparative studies with pancuronium and other muscle relaxants, this study is still incomplete. However, some comparisons between the characteristics of Org NC 45 as obtained in this study with those of pancuronium available in the other studies can be drawn.

The potency of Org NC 45

In our study Org NC 45 0.05 mg kg^{-1} caused a 90–100% depression of the twitch height, which is reasonably close to the 90% blocking dose of pancuronium 0.04 mg kg^{-1} reported by Katz (1971) and in our earlier studies with pancuronium in anaesthetized patients (Agoston et al., 1977; Agoston, Feldman and Miller, 1979). With smaller doses also, the neuromuscular blocking potency of these compounds appears to be similar. Following pancuronium 0.02 mg kg^{-1} (Katz, 1971) the twitch height was depressed by an average of 44% and 68% (Norman, Katz and Seed, 1970a and b respectively), which is of the same order of magnitude as the effects following Org NC 45 0.03 mg kg^{-1} observed in our study (table I). For all practical purposes, we assume that the neuromuscular blocking potency of Org NC 45 approximates to that of pancuronium in anaesthetized patients, and that a dose of 0.05 mg kg^{-1} of both compounds will produce a 90–99% block during which surgeons can operate.

The onset time

The onset time after the administration of Org NC 45 0.05 mg kg^{-1} appears to be considerably shorter (4.5 ± 0.6 min) than that following a comparable dose of pancuronium (7.0 min) observed in our earlier experiments (Agoston et al., 1977). However, with larger doses of both Org NC 45 and pancuronium, there is little difference in onset times. Following the administration of Org NC 45 0.08 mg kg^{-1} the onset time averaged 4 min; this was the same as that of an equal dose of pancuronium (Katz, 1971). After even greater doses (0.1 mg kg^{-1}) of both Org NC 45 and pancuronium, the onset times were still equal. However, the intubating conditions with Org NC 45 were better and developed much faster than with pancuronium at all the above doses.

Intubating conditions

We observed ideal intubating conditions with complete cord relaxation after Org NC 45 in patients with a partial block of 40–60% of the twitch response of adductor pollicis. This compound may paralyse the vocal cords before full relaxation of the limb muscles. This finding is surprising and may be interesting to follow up, since it is generally known that the dose of a neuromuscular blocking drug required to paralyse the laryngeal muscle for satisfactory intubating conditions is usually several times greater than that needed for limb muscle paralysis.

Duration of action

One of the important advantages of Org NC 45 seems to be its short duration of action. With pancuronium the durations until 90% recovery of the control twitch height reported by Katz (1971) averaged 16 min and 58 min after 0.02 mg kg^{-1} and 0.04 mg kg^{-1} respectively. In our study with Org NC 45, the duration to 90% recovery of the control twitch height averaged 15 min after 0.03 mg kg^{-1} and 27 min after 0.05 mg kg^{-1}. These differences in duration are even more pronounced, since both doses of Org NC 45 were 10 µg kg^{-1} greater than the doses of pancuronium in the studies cited above. Norman, Katz and Seed (1970b) observed that the recovery to 50% of the initial twitch response took 12 min and 37 min following doses of 0.02 mg kg^{-1} and 0.05 mg kg^{-1} of pancuronium respectively. Furthermore, following 0.1-mg kg^{-1} doses of pancuronium there was no visible twitch response for at least 43 min. In contrast, the total durations (recovery to 90% of the control twitch height) following Org NC 45 0.1 mg kg^{-1} and 0.12 mg kg^{-1} averaged 44 and 60 min respectively, which compare very favourably with the duration after pancuronium 0.1 mg kg^{-1} reported by Norman, Katz and Seed (1970b). In our earlier studies (Agoston et al., 1977) we found that the recovery to 75% of the initial twitch response after pancuronium 0.1 mg kg^{-1} took 115 min while in this study (in two patients only) the recovery to 90% of control twitch height after the same dose of pancuronium lasted about 150 min. Comparing the durations after different doses of Org NC 45 (table I) with those after equipotent doses of pancuronium, it appears that Org NC 45 has a two-to-three-fold shorter action than pancuronium.

Recovery time

One practical advantage of Org NC 45 is, however, its remarkably short and predictable recovery time. In this study the recovery times from 25 to 75% twitch force of Org NC 45 averaged 9 min and 15 min following single bolus injections of 0.03 mg kg^{-1} and 0.12 mg kg^{-1} respectively (table I), 17 min after repeated maintenance doses following a high initial dose of 0.1 mg kg^{-1} (table II) and 15 min after long-lasting infusions (table III). In this respect Org NC 45 showed a different dynamic behaviour when compared with pancuronium. In a recent study (Agoston, Feldman and Miller, 1979) we investigated the durations and recovery times of the neuromuscular blockade induced by pancuronium using three different methods: the isolated arm technique (in volunteers), single bolus injection and continuous infusion (in anaesthetized patients). In that study we found that, after a neuromuscular blockade of comparable magnitude (approximately 90% twitch height depression), the recovery time was shortest when pancuronium was injected in the isolated arm (10 min) and longest when administered by continuous infusion (46 min); not so with Org NC 45. In similar experimental conditions (namely as a bolus and infusion in anaesthetized patients in this study and as a single bolus in the isolated arm in human volunteers (Bencini, Agoston and Ket, 1980) the mean recovery times of Org NC 45 ranged only between 8 and 17 min, irrespective of the doses and methods of administration.

Cumulation

More comparative clinical studies are required to elucidate any cumulative effects of Org NC 45 after multiple doses. Although the time interval between maintenance doses was dose-dependent (table II), maintenance with equal fractional doses as used in these experiments was required at a remarkably regular rate (fig. 2). However, the wide individual variations of the time intervals between maintenance doses even with equal fractional doses (table II) does not allow predictions of the time schedule needed for administration of this neuromuscular blocking agent over the course of a long operation, if continuous recording of its activity is not possible. Similarly, it is not yet possible to predict the infusion rate for the maintenance of the 90% block because this varies widely between patients (table III).

In conclusion, Org NC 45 in clinical trials had the same order of potency as pancuronium. It produced good to excellent intubating conditions and general muscle paralysis following the administration of 0.08 mg kg^{-1} or greater doses within 90–95 s of its administration. Its duration and recovery time in man is two to three times shorter than that of pancuronium. It showed no cumulative effects even after the administration of several maintenance doses. These findings agree with the animal experimental data described by I. G. Marshall and others (1980) in this supplement.

Although we did not examine the cardiovascular effects in detail, thus far Org NC 45 appears to have no chronotropic or pressor effect in man at any of the doses studied. This is supported by the animal experiments (R. J. Marshall et al., 1980). Thus it represents a distinct improvement over the effects of pancuronium described by Loh (1970) and Kelman and Kennedy (1971).

ACKNOWLEDGEMENTS

We are indebted to Dr R. Sia and Dr I. Richardson for their valuable help and assistance in part of the experiments, to Sr J. Ket for her all-round co-operation, to Mrs R. van Tilburg for secretarial assistance and to Dr D. Savage (Organon Labs) for supply of Org NC 45. Prof Dr D. Langrehr and Prof. Dr H. Wesseling were helpful in discussing the manuscript.

REFERENCES

Agoston, S., Crul, J. F., Kersten, U. W., and Scaf, A. H. J. (1977). Relationship of the serum concentration of pancuronium to its neuromuscular activity in man. *Anesthesiology,* 47, 509.

—— Feldman, S. A., and Miller, R. D. (1979). Plasma concentrations of pancuronium and neuromuscular blockade after injection into the isolated arm, bolus injection, and continuous infusion. *Anesthesiology,* 51, 119.

Bencini, A., Agoston, S., and Ket, J. (1980). Use of the human "isolated arm" preparation to indicate qualitative aspects of a new neuromuscular blocking agent, Org NC 45. *Br. J Anaesth.,* 52, 43S.

Durant, N. N., Marshall, I. G., Savage, D. S., Nelson, D. J., Sleigh, T., and Carlyle, I. C. (1979). The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45, and other pancuronium analogues, in the cat. *J Pharm. Pharmacol.,* 31, 831.

Katz, R. L. (1971). Clinical neuromuscular pharmacology of pancuronium *Anesthesiology,* 34, 550.

Kelman, G. R , and Kennedy, B R. (1971). Cardiovascular effects of pancuronium in man. *Br. J Anaesth.,* 43, 335.

Loh, L. (1970). The cardiovascular effects of pancuronium bromide *Anaesthesia,* 25, 356.

Marshall, I. G., Agoston, S , Booij, L. D. H J., Durant, N. N., and Foldes, F. F. (1980) Pharmacology of Org NC 45 compared with other non-depolarizing neuromuscular blocking drugs. *Br. J. Anaesth.,* 52, 11S.

Marshall, R. J., McGrath, J. C., Miller, R. D., Docherty, J., and Lamar, J.-C. (1980). Comparison of the cardiovascular actions of Org NC 45 with those produced by other non-depolarizing neuromuscular blocking agents in experimental animals. *Br. J. Anaesth.,* 52, 21S.

Norman, J., Katz, R. L., and Seed, R F. (1970a). The neuromuscular blocking actions of pancuronium. *Anaesthesia,* 25, 130.

—— —— —— (1970b). The neuromuscular blocking action of pancuronium in man during anaesthesia. *Br. J Anaesth.,* 42, 702.

BLOCAGE NEUROMUSCULAIRE A L'AIDE D'ORG NC 45, NOUVEAU DERIVE DU PANCURONIUM, SUR DES MALADES ANESTHESIES

Etude pilote

RESUME

On a étudié sur des patients anesthésiés les effets de blocage neuromusculaire du nouvel analogue monoquaternaire du pancuronium: Org NC 45. Aux différentes doses administrées sous la forme de bol intraveineux unique ou de bol initial suivi par plusieurs autres petites doses d'entretien, ou encore d'une infusion continue, Org NC 45 semble être à peu près aussi puissant que le pancuronium, mais il a un début d'action beaucoup plus rapide, une durée d'action considérablement plus courte et un taux de récupération plus rapide que le pancuronium. On n'a constaté aucun effet cumulatif même après que 10 doses d'entretien aient été injectées successivement. Des doses telles que 0,08 mg kg^{-1} ont donné en 90–95 s des conditions idéales permettant l'intubation. Des infusions d'Org NC 45 ont permis un contrôle beaucoup plus facile du blocage neuromusculaire que cela n'a été possible avec le pancuronium. Aucun effet secondaire cardiovasculaire n'a été remarqué, même lorsqu'on a utilisé la dose la plus forte (0,12 mg kg^{-1}). Org NC 45 présente des avantages très nets par rapport au pancuronium et constitue pour l'arsenal des relaxants musculaires utiles du point de vue clinique, une addition qui pourrait avoir une très grande valeur.

DIE NEUROMUSKULÄRE BLOCKIERUNGSWIRKUNG VON ORG NC 45, EINEM NEUEN PANCURONIUM-DERIVAT, BEI NARKOTISIERTEN PATIENTEN

Eine Vorstudie

ZUSAMMENFASSUNG

Die neuromuskulären Blockierungswirkungen des neuen monoquaternären Pancuronium-Derivates Org NC 45 wurden in narkotisierten Patienten untersucht. Verabreicht in unterschiedlichen Dosen intravenos—entweder als Einzelinjektion, als Anfangsinjektion gefolgt von mehreren kleinen Dosen zur Aufrechterhaltung, oder als kontinuierliche Infusion—zeigte sich Org NC 45 also ungefähr so stark wie Pancuronium, aber mit schnellerem Wirkungseinsatz, wesentlich kurzerer Wirkungsdauer und rascherer Erholung als Pancuronium. Es zeigte keine kumulativen Wirkungen, auch nicht nach Verabreichung von 10 Aufrechterhaltungsinjektionen hintereinander. Dosen von 0,08 mg kg^{-1} gewahrten ideale Intubationsbedingungen innerhalb von 90–95 Sekunden. Infusionen von Org NC 45 boten eine wesentlich reibungslosere Kontrolle der neuromuskularen Blockierung als mit Pancuronium. Selbst bei der grössten verwendeten Dosis (0,12 mg kg^{-1}) ergaben sich keine Nebenerscheinungen für Herz und Kreislauf. Die Droge besitz gegenüber Pancuronium eindeutige Vorteile und stellt eine potentiell wertvolle Neuerung unter den klinisch nützlichen Muskelentspannungsmitteln dar.

LA ACCION DE BLOQUEO NEUROMUSCULAR DEL ORG NC 45, QUE ES UN DERIVADO DEL PANCURONIUM, EN PACIENTES ANESTESIADOS

Investigación informativa

SUMARIO

Los efectos de bloqueo neuromuscular del nuevo analógico monocuaternario del pancuronium, el Org NC 45, se han investigado en pacientes anestesiados. La administración de Org Nc 45, bien fuera en diferentes dosis a guisa de bolus intravenoso único o como un bolus inicial seguido por varias dosis pequeñas de mantenimiento o mediante infusión continua, parece ser, aproximadamente, tan potente como el pancuronium, pero su acción es más rápida, el periodo de duración de ésta es más corto y su régimen de recuperación es más rápido que en el caso del pancuronium. No mostró efectos acumulativos ni siquiera después de inyectar 10 dosis sucesivas de mantenimiento. Las dosis de 0,08 mg kg^{-1} proveyeron condiciones ideales de intubación en 90–95 seg. Las infusiones de Org NC 45 hicieron posible un control mucho mas uniforme del bloqueo neuromuscular que el que se obtuvo con el pancuronium. No se apreciaron efectos cardiovasculares secundarios, ni siquiera cuando se administró la mayor dosis de 0,12 mg kg^{-1}. El Org NC 45 posee claras ventajas sobre el pancuronium y representa, a nivel potencial, una valiosa incorporación al armamento de relajantes musculares de utilidad clínica.

Br. J. Anaesth. (1980), **52**, 61S

SHORT COMMUNICATIONS

A NEW NEUROMUSCULAR BLOCKING DRUG, ORG NC 45

A pilot study in man

W. L. M. BAIRD AND D. HERD
Division of Anaesthesia, Royal Infirmary, Glasgow

Some actions of Org NC 45 have been assessed in a pilot study in anaesthetized patients and a comparison has been made with pancuronium under the same conditions. Fourteen patients were studied, their ages ranging from 28 to 65 yr. Ten patients received Org NC 45 and four pancuronium. Only patients ascribed to categories 1 or 2 of the American Association of Anesthesiologists' classification of fitness were included, and care was taken to ensure that they were not receiving any drug therapy which might influence the study. Informed consent to the investigation was obtained from all patients.

All the patients were premedicated with papaveretum alone, approximately 1–1.5 h before anaesthesia. An i.v. infusion of Ringer's Lactate solution was established. Anaesthesia was induced by droperidol and fentanyl i.v. followed 3 min later by a sleep-dose of thiopentone; it was maintained with nitrous oxide and oxygen, supplemented by intermittent doses of fentanyl.

Thereafter, the patients were divided into two groups. In group A, the larynx was sprayed with 4% lignocaine, the trachea was intubated and controlled ventilation was facilitated by the use of fentanyl. The patients in group B were maintained on spontaneous ventilation using a face-mask.

The patient's right arm was extended on an arm-rest and the muscle twitch of the adductor pollicis muscle recorded by means of an Ether U.F.1 force-displacement transducer connected to a Devices pre-amplifier and recorder unit. Supramaximal stimuli at a frequency of 0.1 Hz and duration of 0.2 ms, were applied from a Grass peripheral nerve stimulator via needle electrodes placed close to the ulnar nerve at the wrist. The heart rate was recorded by a Roche 105 E.C.G. monitor throughout each study and the systolic arterial pressure was measured in the usual way by means of a standard sphygmomanometer.

When the control muscle twitch height had been recorded, the patients in group A were given a dose of relaxant which was predicted to produce approximately 90–95% blockade. The precise time of the injection of the drug into the fast flowing i.v. drip was noted and the twitch height recorded throughout the duration of blockade.

The group B patients received a dose of relaxant which was two-and-a-half times that of the 90% blocking dose. Laryngoscopy was performed after 1.5 min, the precise time being noted, and the intubating conditions immediately thereafter were assessed according to the classification described by Lund and Stovner (1970). The muscle twitch was recorded until 100% blockade was established and thereafter the recovery of neuromuscular transmission was followed by the train-of-four technique (Ali, Utting and Gray, 1971).

From the small number of patients studied it would appear that, in approximately equipotent doses, Org NC 45 has a somewhat shorter duration of action compared with pancuronium (fig. 1). There was no evidence of tachycardia with the new compound.

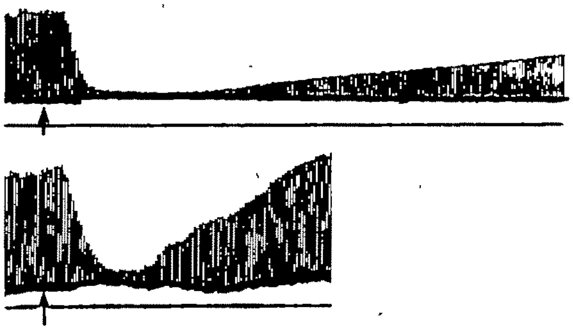


FIG. 1. Upper tracing: 94% neuromuscular blockade produced by pancuronium 0.04 mg kg^{-1}. Lower tracing: 91% neuromuscular blockade produced by Org NC 45 0.03 mg kg^{-1}. (Different patients.)

Table I shows the results from the six patients studied in group A who were given a dose of relaxant which was predicted to produce approximately 90% depression of the evoked twitch height. As would be expected, however, some degree of variation in the individual sensitivity to neuromuscular blocking drugs was evident.

TABLE I. *Results from patients in group A*

	Org NC 45				Pancuronium	
Patient:	1	2	3	4	5	6
Dose (mg kg^{-1})	0.03	0.03	0.03	$0.03+0.01 = 0.04$	0.04	0.04
Twitch depression (%)	91	55	95	50 → 88	94	71
Injection to onset (min)	1.5	2.1	1.8	2.08	3.17	1.57
Onset to max. blockade (min)	1.8	3.9	3.4	8.59	1.0	4.99
Time to 50% recovery (min)	7.0	1.9	22.8	9.83	30.8	11.27
Time to 100% recovery (min)	15.0	12.8	—	16.7	—	19.4

0007–0912/80/130061–09 $01.00

© Macmillan Publishers Ltd 1980

TABLE II. *Results from patients in group B. * After neostigmine 1.25 mg*

	Org NC 45						Pancuronium	
Patient:	1	2	3	4	5	6	7	8
Dose (mg kg^{-1})	0.075	0.075	0.075	0.075	0.075	0.075	0.1	0.1
Injection to onset (min)	1.3	1.1	1.25	0.8	0.9	1.25	0.75	0.92
Onset to 100% block (min)	1.2	1.9	1.05	1.3	1.4	2.42	0.75	1.66
Injection to laryngoscopy (min)	1.83	2.0	1.75	1.5	1.58	1.75	1.55	1.55
Intubating conditions	Satis.	Fair	Satis.	Satis.	Excell.	Fair	Satis.	Excell.
Injection to train-of-four (min)	50	32	60	36	60	43	120	80
Ratio 4th twitch/1st twitch (%)	90	92	72	68	49	92*	26	27

Pressure on surgical time did not permit us to follow patients No 3 and No. 5 to 100% recovery of the twitch height. The prolonged time interval (8.59 min) from onset to maximum blockade in patient No. 4 could be explained by the fact that the initial dose of Org NC 45 0.03 mg kg^{-1} produced only a 50% depression of the twitch height and an additional dose of 0.01 mg kg^{-1} was required to increase the blockade to 88%.

As a result of the group A study and from previous experience with pancuronium, doses of Org NC 45 0.075 mg kg^{-1} and pancuronium 0.1 mg kg^{-1} respectively were selected as representing two-and-a-half times that of the 90% blocking dose and were administered to the eight patients in group B. At the end of the operation the residual neuromuscular blockade was measured using the train-of-four response, noting the time of the recording and the ratio of the fourth twitch to the first twitch expressed as a percentage (table II).

Three of the patients in this group, their train-of-four ratio having spontaneously recovered to 90% or better at the end of anaesthesia, were judged to require no neostigmine. Forty-three minutes after injection of the relaxant, patient No. 6 showed a train-of-four ratio of 92%, neostigmine 1.25 mg having been given 2 min previously. On administration of the same dose of neostigmine to the other four patients, complete recovery of the train-of-four ratio was recorded within a few minutes

Figure 2 shows the absence of tachycardia on injection of an intubating dose of Org NC 45 (0.075 mg kg^{-1}) and although a transient reflex increase in heart rate was seen at the time of endotracheal intubation, within 3 min the rate had returned to approximately 60 beat min^{-1}.

From previous experience of pancuronium and our limited results so far, it would appear that, in the anaesthetized patient, Org NC 45 has a potency of approximately 1.0 to 1.3 times that of pancuronium. The neuromuscular blockade produced by Org NC 45 has a more rapid offset than that of pancuronium in equipotent doses and the blockade is readily antagonized by neostigmine. Unlike pancuronium, Org NC 45 in neuromuscular blocking doses within the clinically useful range, does not appear to produce tachycardia.

ACKNOWLEDGEMENT

We wish to acknowledge the technical assistance received throughout this study from Mr Jim Walls, Chief Technician, and his staff

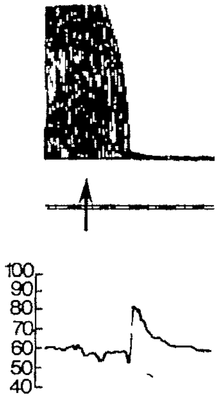


FIG. 2. Neuromuscular blockade produced by Org NC 45 0.075 mg kg^{-1}, showing heart rate changes associated only with endotracheal intubation.

REFERENCES

Ali, H., Utting, J., and Gray, T. C. (1971). Quantitative assessment of residual anti-depolarizing block (Part I). *Br. J. Anaesth.*, **43**, 473.

Lund, I., and Stovner, J. (1970). Dose-response curves for tubocurarine, alcuronium and pancuronium. *Acta Anaesthesiol. Scand.* (Suppl. 37), 238.

THE NEW NON-DEPOLARIZING MUSCLE RELAXANT ORG NC 45 IN CLINICAL ANAESTHESIA: PRELIMINARY RESULTS

W. BUZELLO, G. BISCHOFF, E. KUHLS AND G. NÖLDGE
Institut fur Anaesthesiologie der Univ.-Kliniken, Freiburg, Federal Republic of Germany

Org NC 45 is a recent result of attempts to develop a shorter-acting muscle relaxant with less cardiovascular side-effect than pancuronium. The drug is now under clinical evaluation, and this paper is to report our first results.

Org NC 45 was used in 27 adult patients of ASA classes II–IV undergoing cardiovascular surgery who had no signs of neuromuscular, renal or hepatic disease. The cardiac patients were studied during the pre-bypass period only. All patients received atropine 0.01 mg kg^{-1}, triflupromazine 20 mg and pethidine 50 mg i m. as premedication. Anaesthesia was induced by thiopentone, fentanyl and droperidol i.v. according to individual requirements. Tracheal intubation was performed either under topical anaesthesia or after relaxation with Org NC 45. Anaesthesia was maintained with increments of fentanyl 0.1–0.2 mg under mechanical ventilation with equal parts of oxygen and nitrous oxide. Neuromuscular transmission was monitored by the evoked compound e.m.g. of the adductor pollicis muscle (Lee et al., 1977). The ulnar nerve was stimulated by train-of-four supramaximal square pulses 2 Hz for 0.2 ms, 30 s apart. The tracheal tube was inserted at the time of maximum neuromuscular blockade as displayed by the e.m.g. The e.m.g. tracings were evaluated by expressing the first compound action potential of each train as percentage of control, which provides the same information as single twitch recording, and the train-of-four ratio (T_4) which gives the fourth action potential as a fraction of the first one of the same train.

After Org NC 45 0.075 mg kg^{-1} there were always smooth intubation conditions although movements of the patients' hands or fingers were sometimes observed. There were no significant changes in heart rate and arterial pressure.

The results for onset and recovery are given in table I. The time of onset, the amount of block and the duration to 25% recovery were dose-dependent. The mean 90% blocking dose was 0.06 mg/kg body weight. In all dose ranges increments of the full initial dose at 100% recovery of the twitch response were followed by only moderate cumulation. This was shown by a more rapid onset of action and by an increase of both the amount of block and the duration to 25% recovery. Increments of one-fifth of the initial dose at every 25% recovery created remarkably constant recovery patterns almost without any signs of cumulation. One representative case of each type of incremental dosage is illustrated by figures 1 and 2.

The effect of neostigmine on the recovery from the neuromuscular block produced by Org NC 45 was tested in four cases. The resulting recovery indices of 6±1 min were significantly less than the control figures shown in table I.

The place of this new drug can only be judged in comparison with other available neuromuscular blocking drugs. This is not yet possible in statistically significant terms. However, we have reviewed more than 100 unpublished cases using pancuronium in the same type of patients. A comparison shows the mean 90% blocking dose of pancuronium to be 1.3 times that of Org NC 45. The time of onset by pancuronium 0.075 mg kg^{-1} is 1.4 to 2 times longer and both the duration from the end of injection to 25% recovery and the recovery index are almost three times longer than the corresponding parameters for the same dose of Org NC 45. Additionally, the variability of the effects is less with Org NC 45 than with pancuronium. Since the kinetic parameters of all other non-depolarizing muscle relaxants of clinical significance are more or less within the same range (Buzello and Agoston, 1978), Org NC 45 represents progress towards a more rapid and short-acting drug. Thus Org NC 45 may be used with particular advantage in surgical

TABLE I. *Onset and recovery of Org NC 45-induced neuromuscular blockade (mean ± SD). †Time from end of injection to maximum effect. *Some patients were given additional doses of Org NC 45 before recovery studies were completed*

Dose (mg kg^{-1})	Onset (min)†	Maximum effect (% block)	Duration (min) from end of injection to percent recovery* 25	50	75	100	Recovery index (min)
0.05	5±1 $n=6$	87±12 $n=6$	15±5 $n=6$	18±6 $n=4$	21±2 $n=3$	38 $n=1$	10±1 $n=2$
0.075	5±1 $n=14$	95±8 $n=14$	19±7 $n=11$	22±6 $n=8$	26±8 $n=7$	32±10 $n=7$	8±3 $n=7$
0.1	5±1 $n=7$	100±1 $n=7$	32±7 $n=7$	36±7 $n=4$	41±3 $n=2$	55 $n=1$	11.5 $n=1$

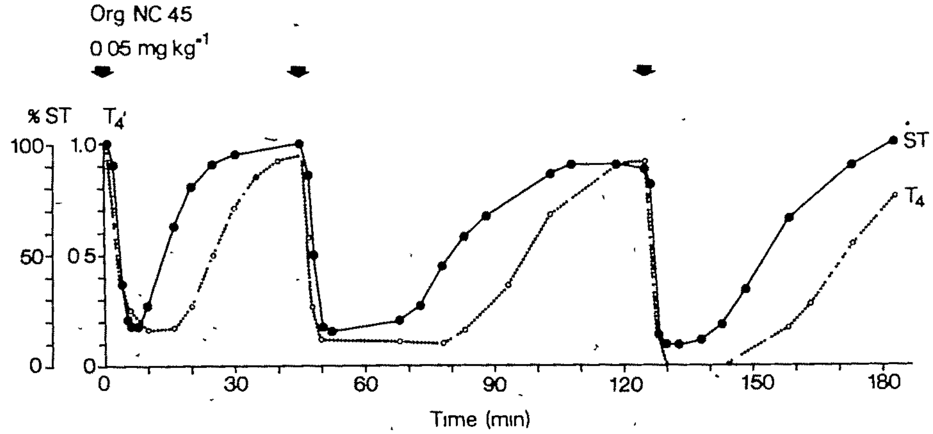


FIG. 1. Moderate cumulation after repeating the full initial dose of Org NC 45 at 100% recovery (ST).

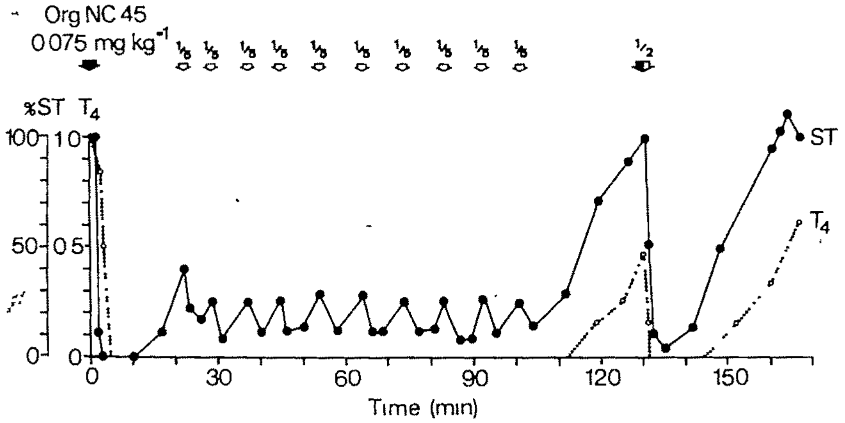


FIG. 2. Repetitive administration of one-fifth of the initial dose at 25% recovery (ST) and one-half at 100% ST.

procedures of short or intermediate duration. The relatively low variation in individual response, the low tendency to cumulation, the relatively short recovery index, and its easy antagonism by neostigmine enable the anaesthetist to maintain neuromuscular block until nearly the end of operation.

Additionally, the drug appears particularly appropriate for patients with cardiovascular disease. Even though it is still far from being the "non-depolarizing suxamethonium" as desired by many anaesthetists, it will certainly fill a gap in our neuromuscular armamentarium if these preliminary findings are confirmed by further clinical studies.

REFERENCES

Buzello, W., and Agoston, S. (1978). Comparative clinical pharmacokinetics of tubocurarine, gallamine, alcuronium and pancuronium. *Anaesthesist*, 27, 313.

Lee, C., Katz, R. L., Lee, A. S. J., and Glaser, B. (1977). A new continuous recording of the evoked compound electromyogram in the clinical setting. *Anesth. Analg.*, (*Cleve.*), 56, 260.

INFLUENCE OF HALOTHANE AND ENFLURANE ON THE NEUROMUSCULAR EFFECTS OF ORG NC 45 IN MAN

F. F. FOLDES,* A. BENCINI AND D. NEWTON
Department of Anaesthesiology, University Hospital, Groeningen, The Netherlands

It is well known that potent inhalation anaesthetic agents increase the neuromuscular effects of muscle relaxants (Foldes, 1959). The influence of various inhalation anaesthetics on the same drug (Miller, Eger and Way, 1971) or that of the same inhalation anaesthetic on different muscle relaxants (Foldes, Sokoll and Wolfson, 1961) may be different. The pilot study reported here was undertaken to determine, before its introduction into clinical practice, the influence of halothane and enflurane on the neuromuscular effects of Org NC 45, a monoquaternary analogue of pancuronium (Durant et al., 1979).

Eight adult patients (ASA classification I and II) were premedicated with droperidol 5 mg or diazepam 10 mg administered i.m. 30–45 min before, and with fentanyl 0.05–0.10 mg and atropine 0.4–0.6 mg injected i.v. immediately before, induction of anaesthesia. Anaesthesia was induced in six patients with additional droperidol 5–10 mg, fentanyl 0.1–0.2 mg and a mixture of nitrous oxide 6 litre and oxygen 3 litre; in two other patients anaesthesia was induced with thiopentone 250 or 350 mg followed by fentanyl 0.05 mg and the same nitrous oxide–oxygen mixture. Additional 0.025 to 0.05-mg increments of fentanyl were administered until the respiratory rate decreased to 12 b.p.m. or less and the patients did not react to auditory stimuli. At this time needle electrodes were inserted near the ulnar nerve at the wrist. The nerve was stimulated with a constant-current nerve stimulator (Model Z-200-M, Rule Medical Instruments, Inc., Pittsfield, Mass.) delivering 0.1-s trains of 50 Hz supramaximal impulses of 0.2 ms duration, every 10 s. The evoked tension of the adductor pollicis muscle was recorded using a Grass FT10 transducer and a Brush recorder. Once the response of the muscle became stabilized the patient was given suxamethonium 0.6 mg kg^{-1} and the trachea was intubated 1 min later. After the tension returned to its control value, Org NC 45 15–20 μg kg^{-1} was administered i.v. to four patients and a steady state of about 50% depression of contractions was maintained by the appropriate i.v. infusion of a solution of Org NC 45 50 μg ml^{-1}. Then 2% halothane was added to the nitrous oxide–oxygen mixture for 5 min followed by 0.5% halothane for 10 min. Fifteen minutes after the discontinuation of the administration of halothane the i.v. infusion of Org NC 45 was also discontinued.

In two other patients an approximated depression of contraction of 90% was induced with a 20 to 30-μg kg^{-1} i.v. dose of Org NC 45 followed by a continuous infusion of a solution of Org NC 45 50 μg ml^{-1}. After the development of the steady state the infusion of Org NC 45 was discontinued and when the tension output again became stable for 5 min, 2% halothane and thereafter 0.5% halothane was added to the inhaled nitrous oxide–oxygen gas mixture. After 10 min of 0.5% halothane Org NC 45 5–10 μg kg^{-1} was injected. This was followed by the infusion of Org Nc 45 50 μg ml^{-1} at a rate required to produce the same degree of neuromuscular block that was obtained earlier without the inhalation of halothane.

---

* Present address: Montefiore Hospital and Medical Center, Department of Anesthesiology, 111 East 210th Street, Bronx, New York 10467, U.S.A.

In two other patients, who in every other respect were managed identically with those of the first halothane group, the influence of the admixture of 4% enflurane for 5 min and 1% enflurane for 10 min was determined.

Figure 1 indicates that the about 40% steady state neuromuscular block induced by the continuous infusion of Org NC 45 increased to about 60% after the addition of halothane.

The difference between the degree of neuromuscular block before and during the inhalation of halothane was significant at the 1% level. Similarly, figure 2 demonstrates that the i.v. dose of Org NC 45 required (μg kg^{-1} h^{-1}) to produce an about 90% steady state block was 25–30% less during the inhalation of halothane than before.

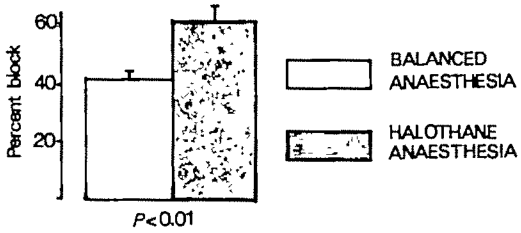


FIG. 1. The intensity of the steady state neuromuscular block induced by identical μg kg^{-1} h^{-1} doses of Org NC 45 in the same patients under balanced or halothane anaesthesia.

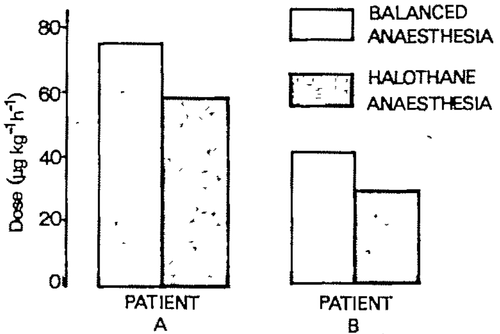


FIG. 2. The doses of Org NC 45 required for greater than 90% steady state neuromuscular block during balanced or halothane anaesthesia in the same two patients.

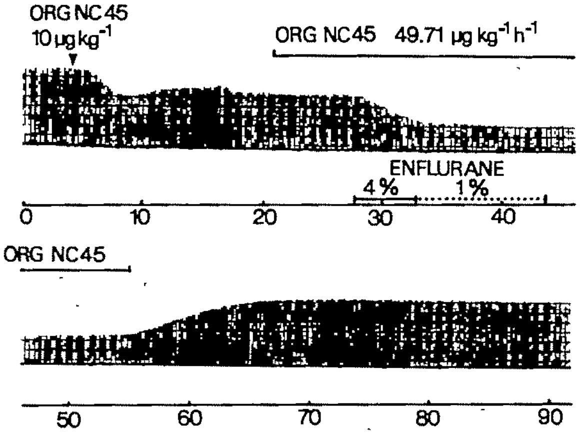


FIG. 3. The influence of enflurane on the intensity of the steady state neuromuscular block induced by Org NC 45 during balanced anaesthesia. Note that the about 30% block increased to about 70% during inhalation of enflurane.

As shown in figure 3, the about 30% steady state block produced by the continuous infusion of Org NC 45 49.71 μg kg^{-1} h^{-1} increased to 75% during the inhalation of enflurane. A similar result was found in the other patient.

The potent inhalation anaesthetic agents, halothane and enflurane, potentiated the effects of Org NC 45 as they do other non-depolarizing neuromuscular blocking drugs. In about anaesthetic concentrations enflurane increased the neuromuscular efffects of Org NC 45 more than halothane. The findings presented suggest that in patients anaesthetized with halothane or enflurane, the doses of Org NC 45 should be about 25 and 45% smaller than those used with balanced anaesthesia.

REFERENCES

Durant, N. N., Marshall I. G., Savage, D. S., Nelson, D. J., Sleigh, T., and Carlyle, I. C. (1979). The neuromuscular and autonomic blocking activities of pancuronium, Org NC 45 and other pancuronium analogues, in the cat. *J. Pharm. Pharmacol.*, **31**, 831.

Foldes, F. F. (1959). Factors which alter the effects of muscle relaxants. *Anesthesiology*, **20**, 464.

—— Sokoll, M., and Wolfson, B. (1961). Combined use of halothane and neuromuscular blocking agents for the production of surgical relaxation. *Anesth. Analg.* (*Cleve.*), **40**, 629.

Miller, R. D., Eger, E. I., and Way, W. L. (1971). Comparative neuromuscular effects of forane and halothane alone and in combination with d-tubocurarine in man. *Anesthesiology*, **35**, 38.

PRELIMINARY CLINICAL OBSERVATIONS WITH ORG NC 45

H. SCHAER AND G. HOSSLI
Kreisspital Männedorf-Zurich, Department of Anaesthesia, University Hospital Zürich

We have used Org NC 45 in 40 patients. It was given in short surgical procedures and the time course of its action was assessed clinically. The routine monitoring of the patients included arterial pressure, heart rate and e.c.g. The anaesthetic technique was either an induction with thiopentone followed by enflurane in nitrous oxide and oxygen or flunitrazepam and fentanyl in nitrous oxide and oxygen. The patients were intubated 2.5 min after Org NC 45 0.07 mg kg^{-1} or 1.5 min after 0.1 mg kg^{-1}. The intubating conditions were satisfactory. In 20 cases the operating procedure lasted less than 25 min, so that the effect of one single dose could be observed. After Org NC 45 0.07 mg kg^{-1}, extubation was always possible 30 min after injecting Org NC 45. Spontaneous respiration was adequate and all patients were able to lift their head without needing neostigmine. Forty minutes after injection of Org NC 45 0.1 mg kg^{-1} spontaneous respiration was also considered clinically adequate, but the patients were unable to lift their head. This residual curarization was always antagonized easily by the adminstration of atropine 0.5 mg and neostigmine 1.0 mg.

No effects on arterial pressure and heart rate were observed which could be attributed to Org NC 45 and no allergic reactions occurred in this small series of patients.

ORG NC 45: INITIAL EXPERIENCES

J. SWEN
Institute of Anaesthesiology, Leiden University Hospital, The Netherlands

Since the introduction of Org NC 45 into our clinic we have studied its action in 12 patients in whom twitches of the adductor pollicis muscle were evoked by stimulating the ulnar nerve through subcutaneous needle electrodes connected to a stimulator delivering stimuli of 0.2 ms duration at a frequency of 0.1 Hz and supramaximal intensity. The twitches were recorded by means of a Statham force transducer (UC 3) attached to a device that was taped into the hand of each patient. All patients were premedicated with atropine 0.5 mg and Thalamonal (droperidol and fentanyl) 1.5–2 ml. All received a "balanced" anaesthetic, after induction with thiopentone 200–250 mg i.v. they were ventilated with a mixture of nitrous oxide and oxygen, and fentanyl 0.05 mg kg^{-1} and droperidol 5–7.5 mg were administered. During the course of the anaesthesia fentanyl 0.1 mg was administered every 30 min. Volatile anaesthetics were not used.

Eight patients were intubated with the aid of suxamethonium 1 mg kg^{-1} and when the effect of suxamethonium had worn off, Org NC 45 was administered either in a dose of 0.07 mg kg^{-1} (four patients) or in a dose of 0.1 mg kg^{-1} (four patients). In a further four patients, suxamethonium was not administered, intubation being carried out with the aid of Org NC 45 0.1 mg kg^{-1}. In all 12 patients, one or more maintenance doses, each initially of Org NC 45 0.02 mg kg^{-1} were injected subsequently. The time courses of the effects of Org NC 45 in the 12 patients are summarized in table I.

In all patients to whom Org NC 45 was administered, kidney and liver functions and electrolyte values were within normal limits.

In general, we concluded that Org NC 45 had a medium rate of onset of action and a consistently short recovery time. The duration of its effect, as with other neuromuscular blocking

TABLE I. *Time course of effects of Org NC 45*

Patient	Intubation with suxamethonium	Initial dose of Org NC 45 (mg kg^{-1})	Time of onset (injection to max. effect) (min)	Duration of maximal effect after first dose (min)	Time from 25% to 75% twitch recovery (min)	Time between maintenance doses of Org NC 45 0.02 mg (min)
1	Yes	0.07	3	7	6	13
2	Yes	0.07	2	12	14	13–18
3	Yes	0.07	5.5	8	14	—
4	Yes	0.07	3	12	9	11–17
5	Yes	0.1	3	38	—	31
6	Yes	0.1	3	16	10	12
7	Yes	0.1	2.5	30	14	—
8	Yes	0.1	2	25	—	12
9	No	0.1	3.5	9	12	14–21
10	No	0.1	6	5	7	9–15
11	No	0.1	3.5	22	10	11–15
12	No	0.1	3	14	—	25–32

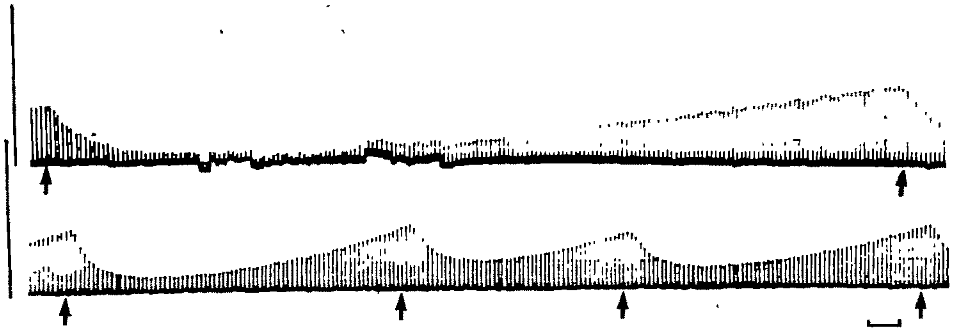


FIG 1. Records from two different patients (patients 5 and 10 of table I). The control twitch amplitudes are indicated by the vertical lines on the left. The effects of maintenance doses (all of Org NC 45 0.02 mg kg^{-1}) are illustrated. In the upper records (patient 5) the effect of the second and the onset of the third maintenance doses are shown. In the lower records (patient 10) the effects of the fifth, sixth, and seventh, and the onset of the eighth maintenance doses are shown. Note that the block produced in patient 5 (upper) was about twice as long as that produced in patient 10. Note also the lack of cumulative effect evident in the lower record. The time calibration is 1 min.

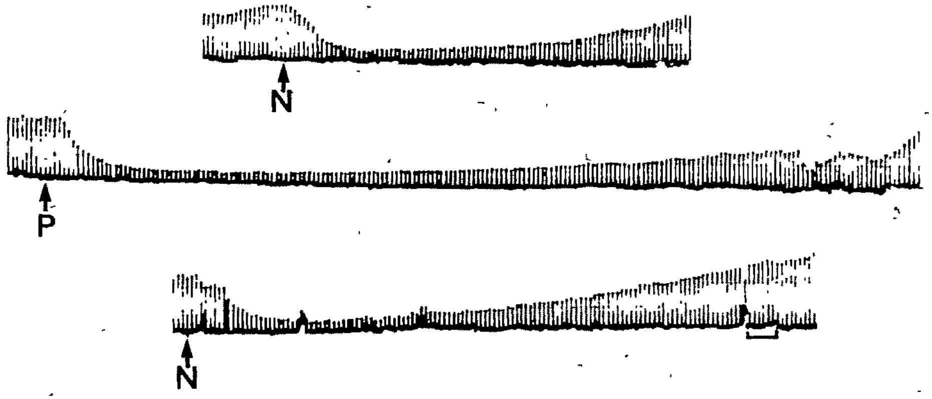


FIG. 2. Records from a patient to whom both Org NC 45 1 mg at N and pancuronium 1.5 mg at P were administered. Note that, for approximately equal degrees of block, recovery from Org NC 45 was considerably faster than that from pancuronium. The time calibration is 1 min.

drugs, was variable. The variation in the duration of block in different patients is illustrated in figure 1. Both patients were of the same age group and both had undergone laparotomy. In each case, the recordings shown were made about 1 h after the commencement of the operation. The body temperatures were 35.2 ° and 35.5 °C measured with a nasopharyngeal probe.

Another facet of the action of Org NC 45, lack of cumulative effect, is also illustrated by the lower record of figure 1.

In one patient we were able to demonstrate the differences in the time courses of action of Org NC 45 and of pancuronium given in equi-active doses. The results are illustrated in figure 2. Org NC 45 was injected both before and after pancuronium. Recovery from Org NC 45 in this patient was about twice as rapid as recovery from pancuronium.

In summary, the limited number of observations suggest that Org NC 45 is about equipotent with pancuronium, it has a medium rate of onset of action, a relatively rapid rate of recovery, and a rather variable duration of action. Little cumulative effect between doses is evident. No cardiovascular side-effects were observed.

ON ORG NC 45 AND HALOTHANE ANAESTHESIA
Preliminary results

J. VIBY-MOGENSEN, B. C. JØRGENSEN, J. ENGBAEK AND B. SØRENSEN
Department of Anaesthesia, Herlev Hospital, University of Copenhagen, Denmark

Animal experiments suggest that the new neuromuscular blocking agent Org NC 45 has a rapid onset and a medium duration of action and is without cardiovascular side-effects. The main purpose of this pilot study of Org NC 45 was to gain an impression of the drug's neuromuscular and cardiovascular effects in normal adult patients anaesthetized with halothane.

The results presented here are preliminary, as the study is still in progress.

Informed consent was obtained from 11 healthy adult patients (five females and six males, aged 35–65 yr) undergoing minor surgical procedures The patients were premedicated with diazepam 0.2 mg kg^{-1} orally 60 min before induction of anaesthesia with i.v. injection of thiopentone 4–5 mg kg^{-1}; suxamethonium 1 mg kg^{-1} was given i.v. to facilitate intubation. Anaesthesia was maintained with nitrous oxide 3 litre in oxygen 3 litre and halothane 0.5–1.0% inspiratory concentration according to the need of the patient. Ventilation was controlled using a Monoghan ventilator delivering a minute volume of 120 ml kg^{-1} min^{-1}.

The ulnar nerve was stimulated electrically at the wrist through percutaneous electrodes connected to a Myotest stimulator (Viby-Mogensen et al., 1980). The adduction force of the thumb twitch was measured by a displacement transducer (Statham UC 3 (gold cell)), and recorded on a Gould Brush 220 recorder. A series of four supramaximal single stimuli (rectangular pulses of 0.2 ms duration) were applied to the nerve at 2 Hz for 2 s every 12 s (train-of-four) as described by Ali, Utting and Gray (1970). When the response to train-of-four nerve stimulation was stable, the height of the first twitch of the train was taken as the standard control (control twitch height).

When "stable halothane anaesthesia" was established 20–30 min after induction of anaesthesia, Org NC 45 0.1 mg kg^{-1} was injected over a period of 10 s in a fast running i.v. infusion.

The onset time (time from the end of injection of Org NC 45 to total disappearance of the twitch response), duration of action (time to first reaction to stimulation, 10% twitch recovery and 50% twitch recovery) and rate of offset (25–75% recovery time) were determined from the train-of-four recordings. In six patients the neuromuscular block was antagonized with neostigmine 0.02 mg kg^{-1} (if needed, twice) preceded by atropine 0.01 mg kg^{-1} at 10% twitch recovery. In five patients the block was allowed to wear off spontaneously.

Heart rate and arterial pressure were recorded every 5 min during the whole procedure and every 2 min in the first 10 min following the injection of Org NC 45. E.c.g. was continuously monitored. Systolic time intervals (four patients) were determined from simultaneous fast-speed recordings of the e.c.g., the phonocardiogram and the carotid arterial pulse tracing (Weissler, Harris and Schoenfeld, 1969) before induction, twice at "stable anaesthesia" before injection of Org NC 45 and

TABLE I. *Onset time and duration of action of Org NC 45, pancuronium and suxamethonium. See text for further explanation.* $^{*}P < 0.01$ *(Kruskal–Wallis test)*

Drug	No. of patients	Dose (mg kg^{-1})	Onset time (s) Mean ± SD	Onset time (s) Range	Time to first reaction to train-of-four (min) Mean ± SD	Time to first reaction to train-of-four (min) Range
Org NC 45	11	0.1	77.4±16.5*	50–100	32.3±10.4*	19.2–53.0
Pancuronium	20	0.1	124.0±55.0*	70–320	59.9±13.7*	33.0–88.0
Suxamethonium	25	1.0	40.3±15.7*	22–90	5.8±2.1*	4.0–8.5

TABLE II. *Systolic time intervals (ms) before and after the injection of Org NC 45 0.1 mg kg^{-1}. PEP = pre-injection period; LVET = left ventricular ejection time*

Patient No.	Systolic time interval	Before induction	Before injection of Org NC 45: 1	Before injection of Org NC 45: 2	Time after injection of Org NC 45 (min): 1	3	8	18	28
1	PEP	112	138	165	160	160	145	126	135
	PEP/LVET	0.34	0.41	0.54	0.50	0.50	0.44	0.35	0.37
2	PEP	80	104	103	97	101	104	95	94
	PEP/LVET	0.26	0.38	0.38	0.33	0.34	0.34	0.29	0.30
3	PEP	—	132	127	123	127	130	118	118
	PEP/LVET	—	0.44	0.41	0.40	0.41	0.41	0.36	0.36
4	PEP	90	138	133	130	105	104	107	104
	PEP/LVET	0.30	0.49	0.47	0.45	0.32	0.32	0.33	0.32

1, 3, 8, 18, and 28 min, respectively after the injection. Blood-gas analyses and end-tidal halothane concentrations (Pye Series 104 Chromatograph, Pye Unicam) were measured at appropriate intervals to secure normal Pa_{CO_2}, pH and "stable halothane anaesthesia"

Table I shows the onset time and time to first reaction to nerve stimulation following Org NC 45 0.1 mg kg^{-1}. For comparison corresponding figures for pancuronium 0.1 mg kg^{-1} and suxamethonium 1.0 mg kg^{-1} have been included in the table. (The doses of Org NC 45 and pancuronium are not equipotent: Org NC 45 is probably 1.3 to 1.5 times as potent as pancuronium in humans.) Mean time (and range) to 10% ($n = 11$) and 50% ($n = 5$) twitch recovery were 39.5 min (22.5–66.7) and 56.7 min (30.0–105.0), respectively. Mean recovery time ($n = 5$) was 31.0 min (14.2–69.6). Org NC 45 was easily reversed from 10% twitch recovery in all six patients given neostigmine. Mean time to 100% twitch recovery was 10.5 min (range: 8.2–16.6).

There were no significant changes in heart rate or arterial pressure following injection of Org NC 45, nor was there any decrease in myocardial performance (table II). Increases in PEP and PEP/LVET denote the presence of diminished left ventricular function. Decreases in PEP and PEP/LVET may indicate a positive inotropic effect (Weissler, 1977) The increase in PEP and the increase in PEP/LVET when halothane was added signified the well-known myocardial depression caused by the anaesthetic agent (Rasmussen and Sørensen, 1975).

The mean end-tidal halothane concentration at the time of injection of Org NC 45 was 0.5 vol% (range 0.3–0.9). The smallest and largest measured concentrations after the injection of Org NC 45 were 0.3 and 0.9 vol%. Mean Pa_{CO_2} was 4.7 kPa (range 3.8–6.1) and the range for pH was 7.34–7.48.

Although we have had the opportunity to investigate only a limited number of patients until now, the results hitherto indicate that further clinical investigations are worth while. Org NC 45 seems to have a shorter onset time and duration of action than pancuronium. The doses investigated (Org NC 45 0.1 mg kg^{-1} and pancuronium 0.1 mg kg^{-1}) were not equipotent. The possibility therefore exists that an increase in dose of pancuronium to 0.13 mg kg^{-1} (equipotent with NC 45 0.1 mg kg^{-1}) may cause a decrease in onset time. However, an increase in dose would cause an increase in duration of action, thus making the difference in duration of action between the two drugs even more pronounced.

Our results also indicate that the remarkable cardiovascular stability following injection of Org NC 45 seen in animal experiments also applies to healthy adult patients.

REFERENCES

Ali, H. H., Utting, J. E., and Gray, T. C. (1970). Stimulus frequency in the detection of neuromuscular block in humans. *Br. J. Anaesth.*, **42**, 967.

Rasmussen, J. P., and Sørensen, B. (1975). Cardiac function during halothane and fluroxene anaesthesia expressed by systolic time intervals. *Acta Anaesthesiol. Scand.*, **19**, 104.

Viby-Mogensen, J., Hansen, P. H., Jørgensen, B. C., Ørding, H., Kann, T., and Fries, B. (1980) A new nerve stimulator (Myotest). *Br. J. Anaesth.*, **52**, 547

Weissler, A. M. (1970). Current concepts in cardiology, systolic time intervals *N. Engl J. Med.*, **296**, 321

—— Harris, W. S , and Schoenfeld, C. D (1969). Bedside technics for the evaluation of ventricular function in man. *Am J Cardiol.*, **23**, 577.

Br. J. Anaesth. (1980), 52, 71S

ORG NC 45

SUMMARY

What is an ideal or perfect neuromuscular blocking drug? The chemists must know what properties an anaesthetist desires before a new compound can be designed. My conversations with chemists indicate that designing the ideal drug is difficult, not only from a chemical point of view, but also because anaesthetists often do not agree on what makes an ideal blocking drug. In spite of such disagreements, Karis and Gissen (1971) defined what they believed the ideal properties a new drug should have. I will assess how closely Org NC 45 meets these requirements.

(1) The neuromuscular blocking drug should be competitive and non-depolarizing. Although the precise mechanism of action of Org NC 45 has not been determined, it has all the necessary characteristics. Thus, the increases in intraocular pressure, electrolyte abnormalities and the muscle pains associated with depolarizing agents should not occur with Org NC 45.

(2) The cessation of neuromuscular blockade should not depend on renal or hepatic function since diseases of the kidney and liver may impair elimination of the drug. Studies in the cat (Durant, Houwertjes and Agoston, 1979a) indicate that impaired function of the liver may indeed prolong the actions of Org NC 45 and pancuronium equally. However, absence of renal function had little or no effect on neuromuscular blockade produced by Org NC 45, whereas that produced by pancuronium was prolonged (Durant, Houwertjes and Agoston, 1979b). Whether impaired liver and kidney function alters the neuromuscular blockade of Org NC 45 in man has not been determined. However, these animal studies indicate that renal failure may prolong an Org NC 45 neuromuscular blockade *less* than that of pancuronium. If so, then Org NC 45 has an advantage over pancuronium in patients with renal failure.

(3) Chemical decomposition of the drug in the body would be acceptable provided the breakdown products do not possess neuromuscular blocking power or produce other unwanted effects. Although the metabolites of Org NC 45 have neuromuscular blocking properties, the extent to which Org NC 45 is metabolized has not been determined and therefore it is not known whether the breakdown products may contribute to the neuromuscular blockade of Org NC 45.

(4) The drug should have a relatively short duration of action. When a longer duration is desired, repeated or continuous administration can be used. With such usage, lack of cumulative effects would be desirable. In this regard, Org NC 45 has a shorter duration of action and has less cumulative effects than other non-depolarizing neuromuscular blocking drugs used in clinical anaesthesia.

(5) It should be highly specific, so that no harmful effects on other systems would occur. Although the effect of Org NC 45 on all organ systems has not been studied, it clearly has little or no cardiovascular effects, unlike nearly all other non-depolarizing muscle relaxants (Booij, Edwards et al., 1980). For example, tubocurarine causes hypotension and pancuronium causes tachycardia. In this regard, Org NC 45 appears to be a "clean" drug as far as cardiovascular effects are concerned.

(6) The neuromuscular blockade should be antagonized easily by acetylcholinesterase inhibitors. Org NC 45 requires about the same dose of neostigmine as that required for antagonism of other commonly used non-depolarizing muscle relaxants (Booij, van der Pol et al., 1980).

In summary, Org NC 45 appears to have clear advantages over present clinically used muscle relaxants. It has a shorter duration of action, less cumulative effects and little or no cardiovascular effects. These advantages support a decision to proceed with more extensive clinical trials.

R. D. Miller

REFERENCES

Booij, L. D. H. J., Edwards, R., Sohn, Y. J., and Miller, R. D. (1980). Comparative cardiovascular effects of Org NC 45, d-tubocurarine, pancuronium and metocurarine. *Anesth. Analg.* (*Cleve.*), 59, 26.

—— van der Pol, F., Crul, J. F., and Miller, R. D. (1980). Antagonism of Org NC 45 neuromuscular blockade by neostigmine, pyridostigmine and 4-aminopyridine and their combinations. *Anesth. Analg.* (*Cleve.*), 59, 31.

Durant, N. N., Houwertjes, M. C., and Agoston, S. (1979a). Hepatic elimination of Org NC 45 and pancuronium. *Anesthesiology*, 51, S267.

——— ——— ——— (1979b) Renal elimination of Org NC 45 and pancuronium. *Anesthesiology*, 51, S266.

Karis, J. H., and Gissen, A. J. (1971). Evaluation of new neuromuscular blocking agents. *Anesthesiology*, 35, 149.

British Journal of Anaesthesia

Editor of General Issues: A. A. Spence

For premedication

In intravenous anaesthesia

For post-operative pain

pentazocine regd.

versatile non-narcotic strong analgesic

injection · tablets · capsules · suppositories

(Misuse of Drugs Act) regulations

Full information on the uses of Fortral in anaesthesia, alone or in combination with sedatives and tranquillisers, available from the Medical Information Department, Winthrop Laboratories, Surbiton-upon-Thames, Surrey. Clinical reports available on request. Fortral is a registered trade mark.

WINTHROP

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52 *Published monthly* SUPPLEMENT 1, 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27.50, Airmail £50 ISSN 0007–0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

ORG NC 45

PAGE

INTRODUCTION: *J. Norman and W. C. Bowman* . . 1S

SYMPOSIUM ON ORG NC 45

The emergence of Org NC 45, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methyl-piperidinium bromide, from the pancuronium series . . 3S
D. S. Savage, T. Sleigh and I. Carlyle

ADDENDUM: The pharmaceutical formulation of Org NC 45 . . 7S
H. Burger, J. Egberink and J. Lakeman

Pharmacology of Org NC 45 compared with other non-depolarizing neuromuscular blocking drugs . . 11S
I. G. Marshall, S. Agoston, L. H. D. J. Booij, N. N. Durant and F. F. Foldes

Comparison of the cardiovascular actions of Org NC 45 with those produced by other non-depolarizing neuromuscular blocking agents in experimental animals 21S
R. J. Marshall, J. C. McGrath, R. D. Miller, J. R. Docherty and J.-C. Lamar

Preliminary review of the interactions of Org NC 45 with anaesthetics and antibiotics in animals. . . 33S
N. Krieg, J. M. J. Rutten, J. F. Crul and L. H. D. J. Booij

Pharmacokinetics and pharmacodynamics of Org NC 45 in man . . 37S
F. van der Veen and A. Bencini

Use of the human "isolated arm" preparation to indicate qualitative aspects of a new neuromuscular blocking agent, Org NC 45 . . 43S
A. Bencini, S. Agoston and J. Ket

PAGE

First clinical experiences with Org NC 45 49S
J. F. Crul and L. H. D. J. Booij

The neuromuscular blocking action of Org NC 45, a new pancuronium derivative, in anaesthetized patients. *A pilot study*. . . 53S
S. Agoston, P. Salt, D. Newton, A. Bencini, P. Boomsma and W. Erdmann

SHORT COMMUNICATIONS

A new neuromuscular blocking drug, Org NC 45. *A pilot study in man*. . . 61S
W. L. M. Baird and D. Herd

The new non-depolarizing muscle relaxant Org NC 45 in clinical anaesthesia. *Preliminary results* . . 62S
W. Buzello, G. Bischoff, E. Kuhls and G. Noldge

Influence of halothane and enflurane on the neuromuscular effects of Org NC 45 in man . . 64S
F. F. Foldes, A. Bencini and D. Newton

Preliminary clinical observations with Org NC 45 . . 65S
H. Schaer and G. Hossli

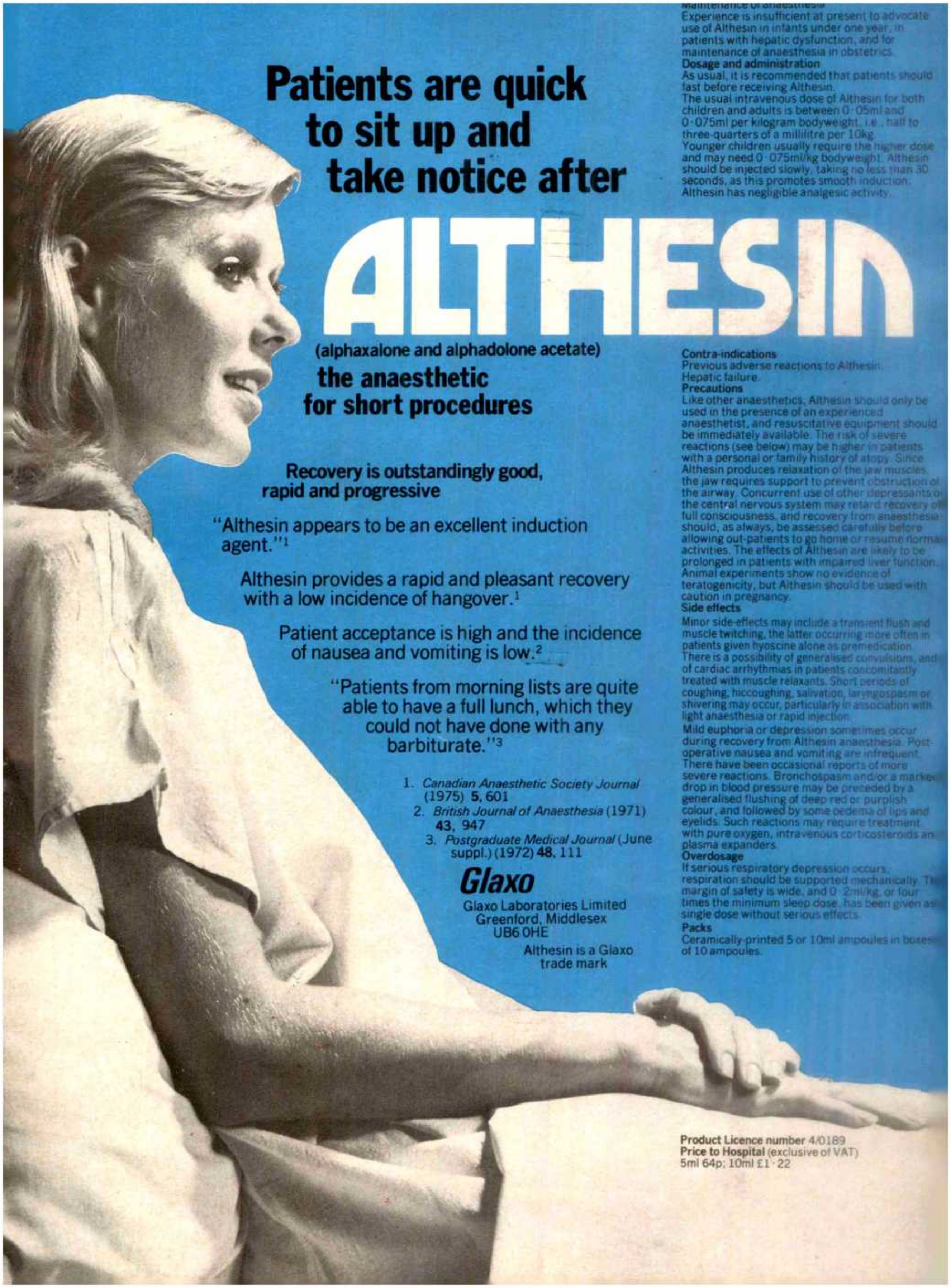
Org NC 45: initial experiences . . 66S
J. Swen

On Org NC 45 and halothane anaesthesia 67S
J. Viby-Mogensen, B. C. Jørgensen, J. Engbæk and B. Sørensen

SUMMARY: *R. D. Miller*. . . 71S

© SCIENTIFIC & MEDICAL DIVISION, MACMILLAN PUBLISHERS LTD.

Printed in Great Britain by John Wright and Sons Ltd. at The Stonebridge Press, Bristol BS4 5NU



Patients are quick to sit up and take notice after ALTHESIN

(alphaxalone and alphadolone acetate)

the anaesthetic for short procedures

Recovery is outstandingly good, rapid and progressive

"Althesin appears to be an excellent induction agent."[1]

Althesin provides a rapid and pleasant recovery with a low incidence of hangover.[1]

Patient acceptance is high and the incidence of nausea and vomiting is low.[2]

"Patients from morning lists are quite able to have a full lunch, which they could not have done with any barbiturate."[3]

1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

Glaxo

Glaxo Laboratories Limited
Greenford, Middlesex
UB6 0HE

Althesin is a Glaxo trade mark

Maintenance of anaesthesia
Experience is insufficient at present to advocate use of Althesin in infants under one year, in patients with hepatic dysfunction, and for maintenance of anaesthesia in obstetrics.

Dosage and administration
As usual, it is recommended that patients should fast before receiving Althesin.
The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e., half to three-quarters of a millilitre per 10kg.
Younger children usually require the higher dose and may need 0·075ml/kg bodyweight. Althesin should be injected slowly, taking no less than 30 seconds, as this promotes smooth induction.
Althesin has negligible analgesic activity.

Contra-indications
Previous adverse reactions to Althesin.
Hepatic failure.

Precautions
Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants o the central nervous system may retard recovery o full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume norma activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects
Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, and of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post-operative nausea and vomiting are infrequent. There have been occasional reports of more severe reactions. Bronchospasm and/or a marke drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids an plasma expanders.

Overdosage
If serious respiratory depression occurs, respiration should be supported mechanically. T margin of safety is wide, and 0·2ml/kg, or four times the minimum sleep dose, has been given as single dose without serious effects.

Packs
Ceramically-printed 5 or 10ml ampoules in boxe of 10 ampoules.

Product Licence number 4/0189
Price to Hospital (exclusive of VAT)
5ml 64p; 10ml £1·22

EDITORIAL BOARD

Editor of General Issues

A. A. Spence, *Reader, University Department of Anaesthesia, Western Infirmary, Glasgow*

Editor of Postgraduate Educational Issues

J. Norman, *Professor of Anaesthetics, The General Hospital, Tremona Road, Southampton SO9 4XY*
C. M. Conway, *Professor of Anaesthesia, Westminster Hospital, London*
E. A. Cooper, *Professor of Anaesthesia, University of Newcastle upon Tyne; Honorary Consultant Anaesthetist, Newcastle University Hospitals*
J. W. Dundee, *Professor of Anaesthesia, Queen's University of Belfast*
F. R. Ellis, *Reader in Anaesthesia, University of Leeds*
W. Fitch (Assistant Editor), *Senior Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*
G. M. Hall, *Senior Lecturer in Anaesthetics, University of London, Royal Postgraduate Medical School*
C. J. Hull, *Senior Lecturer in Anaesthesia, University of Newcastle*
A. R. Hunter (Chairman), *Professor of Anaesthesia, University of Manchester*
D. G. McDowall, *Professor of Anaesthesia, University of Leeds*
W. W. Mapleson, *Professor of the Physics of Anaesthesia, Welsh National School of Medicine, University of Wales*
J. F. Nunn, *Head of Division of Anaesthesia, Clinical Research Centre, Harrow; Honorary Consultant Anaesthetist, Northwick Park Hospital*
J. P. Payne, *British Oxygen Research Professor of Anaesthetics, Royal College of Surgeons of England*
C. Prys-Roberts, *Professor of Anaesthetics, University of Bristol*
J. E. Riding (Hon. Treasurer), *Consultant Anaesthetist, United Liverpool Hospitals; Honorary Lecturer in the Department of Anaesthesia, University of Liverpool*
J. G. Robson, C.B.E. *Professor of Anaesthetics, University of London, Royal Postgraduate Medical School*
D. B. Scott, *Consultant Anaesthetist, Royal Infirmary Edinburgh*
G. Smith, *Professor of Anaesthesia, The General Hospital, Leicester*
M. K. Sykes, *Professor of Clinical Anaesthesia, Royal Postgraduate Medical School, London*

Editorial Assistants

Kirsteen M. S. Dewar, *Consultant Anaesthetist, Western Infirmary, Glasgow*
G. N. C. Kenny, *Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*

Papers for publication and all editorial communications should be addressed to the Editor, University of Glasgow, Department of Anaesthesia, Western Infirmary, Glasgow G11 6NT; business communications to the publishers: Macmillan Journals Ltd, 4 Little Essex Street, London WC2R 3LF.
The GUIDE TO CONTRIBUTORS can be found on pages x, xii & xiv of the advertisement section of this issue.
Published monthly. Annual subscriptions: U.K. £22·50, U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27·50, Airmail £50; (or equivalent in any other currency). ISSN 0007–0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.
Overseas subscribers may make payments into U.K. Post Office Giro Account No. 519 2455. Full details must accompany the payment.
Second Class Postage Paid New York, N.Y. U.S. Mailing Agent: Expediters of the Printed Word, Ltd, PO Box 1305, Long Island City, N.Y. 11101.

All enquiries concerning advertising should be addressed to Advertisement Department, Macmillan Journals Ltd, 3 Dyers Buildings, Holborn, EC1N 2NR (Telephone 01-831 6901). © Copyright: Macmillan Journals Ltd, 1980.

Regional Anaesthesia Update 1980

Acc.
12.9.80

International Symposium
Heidelberg, W. Germany
September 22-25, 1980

Sponsored by
American Society of Regional Anesthesia
German Society of Anaesthesia and Intensive Care Medicine

Invited Faculty:

E. Armitage
H. Bergmann
R. Boas
J. Bonica
D. Bridenbaugh
P. Bridenbaugh
P. Bromage
H. Carron
B. Covino
S. Crawford
R. DeJong
M. Finster
A. Hollman
J. Katz
B. Löfström
P. Lund
D. Moore
H. Niesel
H. Nolte
G. Ostheimer
P. Raj
S. Shnider
O.H. Schulte-Steinberg
B. Scott
D. Selander
M. Stanton-Hicks
M. Swerdlow
A. Winnie

Topics:

Local Anesthesia
Surgical Regional Anesthesia
Obstetrical Regional Anesthesia
Regional Anesthesia for Pain Control

World Federation of Societies of Anesthesiologists
precedes Symposium in Hamburg, G.F.R., Sept. 14-21, 1980

Regional Anaesthesia Update 1980

International Symposium
Heidelberg, W. Germany
September 22-25, 1980

For Information, mail to:

P.P. Raj, M.D.
P.O. Box 11083
Richmond, Va. 23230, USA

Hans Nolte, M.D.
Institut Für Anaesthesiologie
4950 Minden, Wesf., G.F.R.

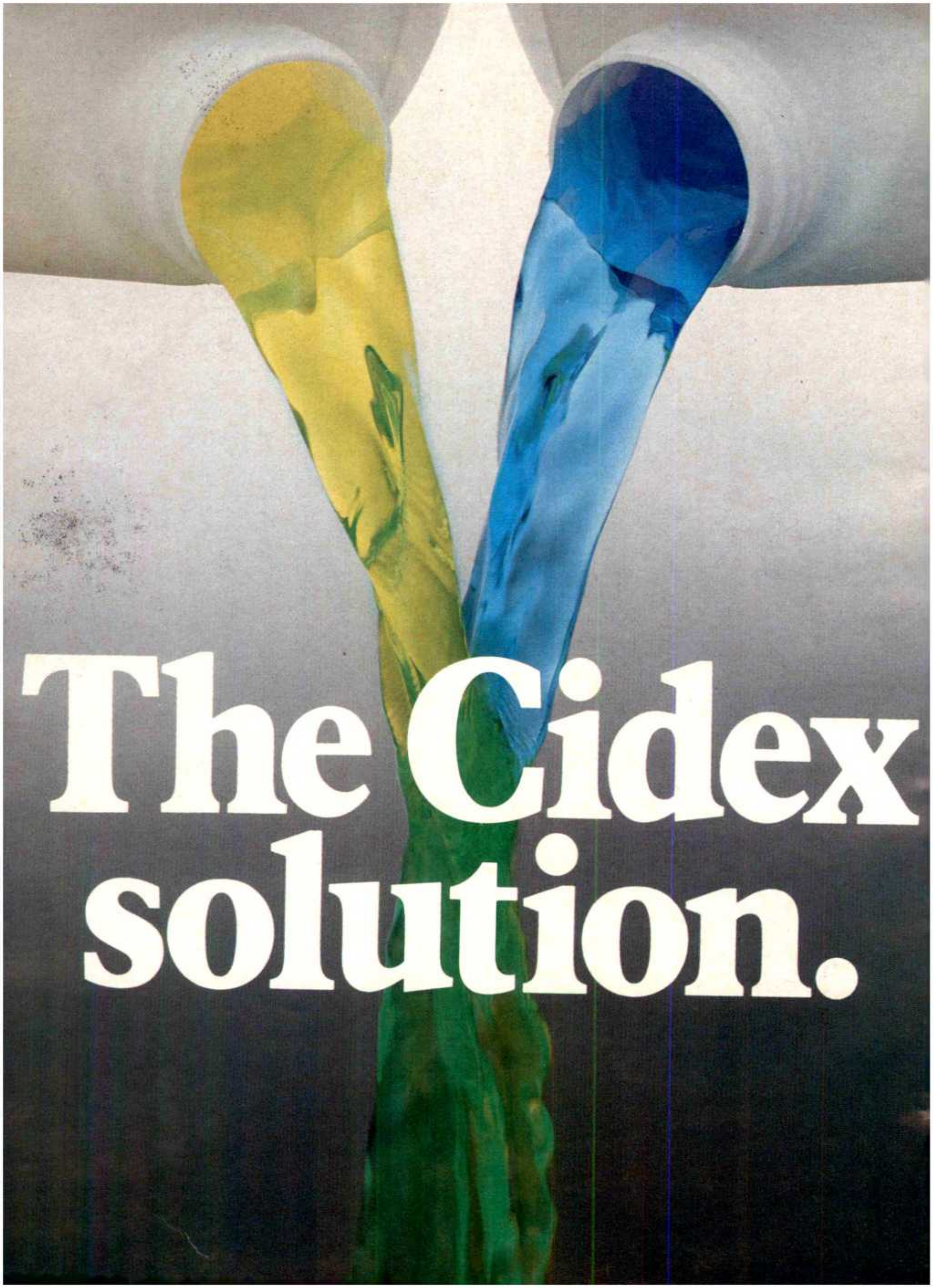
(PLEASE PRINT)

Name ______________________________

Address ______________________________

City/State/Zip/Country ______________________________

☐ ASRA Member ☐ Send ASRA Membership Information


The Cidex solution.

It has long been recognised that different hospitals have different disinfection and sterilization requirements.

These differences, of course, arise from the degree of contamination present, the type of equipment and rate of throughput, and the cleaning/drying procedures used.

What hasn't been recognised sufficiently up till now is that these factors combine to have a cumulative effect on the use-life of cold disinfectant solutions–creating a need for solutions with different use-lives.

To meet this need there are now two solutions.

–CIDEX* Activated Glutaraldehyde Solution with a use-life of up to 14 days.

–CIDEX* Long-Life Activated Glutaraldehyde Solution with a use-life of up to 28 days.

New CIDEX* Long-Life Solution has all the trusted and well-proven benefits of 14 day CIDEX* Solution but has an effective life of 28 days where usage factors permit.

A fresh peppermint odour and blue colour differentiate CIDEX* Long-Life from green 14 day CIDEX* Solution.

WHICH CIDEX* SOLUTION TO USE

While the effects of dilution and gross protein contamination are always present, these can be minimal due to low throughput.

Under these circumstances, new CIDEX* Long-Life Solution is much more convenient and can offer substantial cost savings.

In a busy unit, however, where pressures generally do not permit drying, protein contamination and dilution can build up over a period–particularly with bulky items, such as anaesthetic tubing, which have a high carry-over of water.

In situations such as this, 14 day CIDEX* Solution offers complete assurance of its efficacy, assurance which has been confirmed repeatedly all over the world.

CIDEX* SOLUTIONS. NOT ONLY A CHOICE BUT A BETTER CHOICE

Both solutions have the complete range of cidal activity which has made CIDEX* Solution the prime agent of choice for disinfection and sterilization of heat sensitive and delicate equipment.

Both have the remarkable non-corrosive properties which in laboratory tests have proven them to be less corrosive than deionised water.

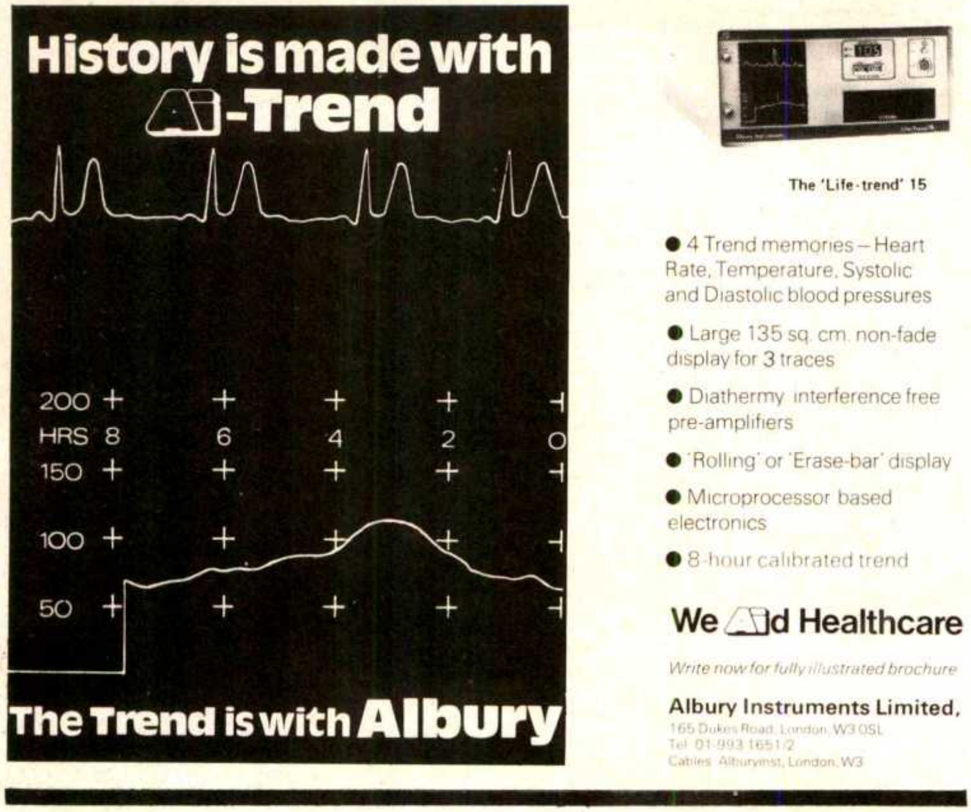
14 day CIDEX* Solution in the green container. 28 day CIDEX* Long-Life Solution in the blue container.

Whatever your choice, you can be confident that CIDEX* is the safest, most cost-effective solution to your disinfecting or sterilizing problem.

A choice of CIDEX* solutions from Arbrook – now you can choose wisely.

Arbrook*

Arbrook Products Limited, Livingston, Scotland EH54 7AT *Regd. Trademark © Arbrook Products Limited 1979.



History is made with Ai-Trend

The Trend is with Albury

The 'Life-trend' 15

- 4 Trend memories – Heart Rate, Temperature, Systolic and Diastolic blood pressures
- Large 135 sq. cm. non-fade display for 3 traces
- Diathermy interference free pre-amplifiers
- 'Rolling' or 'Erase-bar' display
- Microprocessor based electronics
- 8-hour calibrated trend

We Aid Healthcare

Write now for fully illustrated brochure

Albury Instruments Limited,
165 Dukes Road, London, W3 0SL
Tel 01-993 1651/2
Cables Alburyinst, London, W3

STATE UNIVERSITY OF NEW YORK

Upstate Medical Center

The Department of Anesthesiology invites inquiries from Anaesthetists qualified for Assistant or Associate Professorship. An interest in regional anaesthesia, pain therapy or intensive care is desirable but not essential. Highly competitive stipend and fringe benefits. Applicants should have the F.F.A., V.E.Q. and E.C.F.M.G. Send curriculum vitae to:

Howard L. Zauder, M.D., Ph.D.
Professor and Chairman
Department of Anesthesiology
State University of New York
Upstate Medical Center
750 East Adams Street
Syracuse, New York 13210

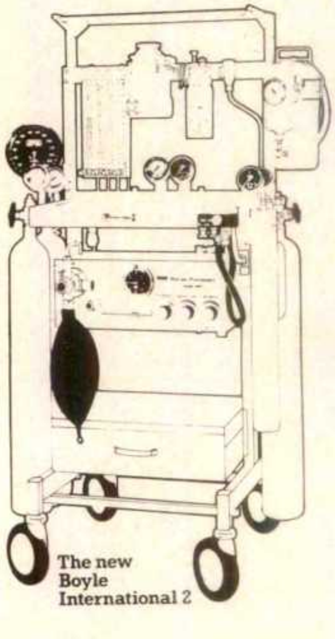
Announcing enormous wait reductions

Boyle anaesthetic machines, suction equipment, oxygen therapy equipment... the products you've been waiting for are now available either ex-stock, or within a steadily reducing delivery period.

Medishield have earned a deserved reputation for quality and dependability; happily we are, once more, able to maintain this reputation, and give you the prompt service which you expect.

For detailed information on delivery of specific products please contact:

BOC (Medishield)
Priestley House, 12 Priestley Way
London NW2 7AG. Telephone: 01-450 8955



The new Boyle International 2

Medishield

depend on Medishield

SIEMENS

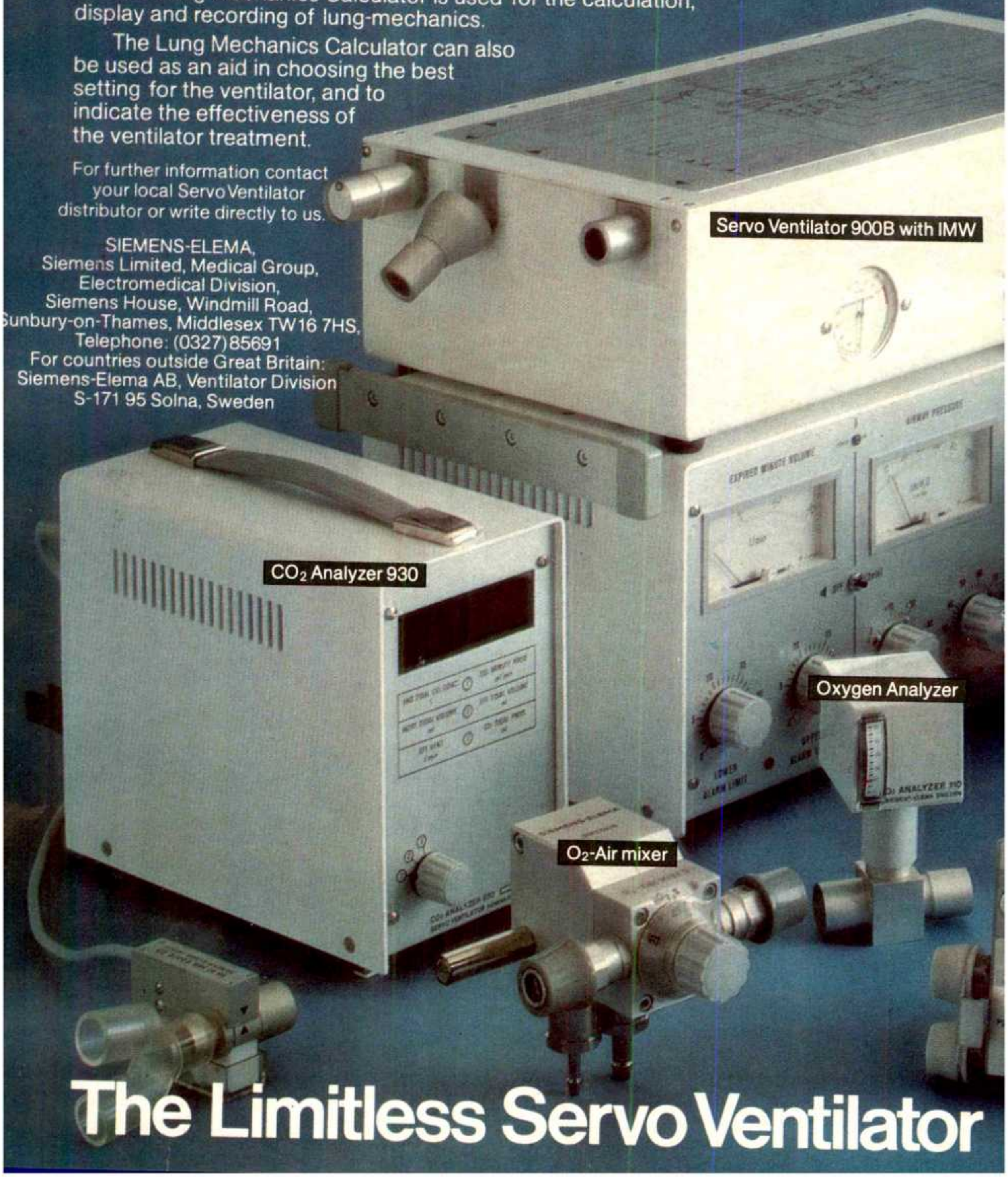
The Lung Mechanics Calcu Servo Ventilator treatment

The Lung Mechanics Calculator is used for the calculation, display and recording of lung-mechanics.

The Lung Mechanics Calculator can also be used as an aid in choosing the best setting for the ventilator, and to indicate the effectiveness of the ventilator treatment.

For further information contact your local Servo Ventilator distributor or write directly to us.

SIEMENS-ELEMA,
Siemens Limited, Medical Group,
Electromedical Division,
Siemens House, Windmill Road,
Sunbury-on-Thames, Middlesex TW16 7HS,
Telephone: (0327) 85691
For countries outside Great Britain:
Siemens-Elema AB, Ventilator Division
S-171 95 Solna, Sweden



The Limitless Servo Ventilator

ator indicates
efficiency.
SERVO VENTILATOR 900B
Alarm Unit 920
O₂-N₂O/O₂-Air mixer
Vaporizer
PEEP valve
0-20 cm H2O
072 015
PEAK PRESSURE cm H2O
① PAUSE PRESSURE cm H2O
INSP. RESISTANCE cm H2O/l/s
② EXP. RESISTANCE cm H2O/l/s
COMPLIANCE ml/cm H2O
③ END EXP. LUNG PRESSURE cm H2O
CONNECTION VOLUME
SMALL
LARGE
LUNG MECHANICS CALCULATOR 940
SERVO VENTILATOR
SIEMENS-ELEMA SWEDEN
System.

SUBSCRIBE TO ANAESTHESIA & INTENSIVE CARE

Published quarterly by the Australian Society of Anaesthetists. Subscription rate 1980 $Aust.28.00. ($US33.00, £Stg.15), back issues/individual copies $Aust.7.00 ($US8.50, £Stg.4.50).

Please send your subscription request to: ANAESTHESIA AND INTENSIVE CARE,
P.O. BOX 525, POTTS POINT, N.S.W. 2011, AUSTRALIA.

Name ______________________________

Address ______________________________

____

Country ______________ Code ______________

Send no money at this stage. We will invoice you and commence your subscription with the current issue.

September 14–21, 1980

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS
7th WORLD CONGRESS OF ANAESTHESIOLOGISTS
HAMBURG

Federal Republic of Germany

Deadline for submission of abstracts: January 31, 1980

Deadline for registration: May 31, 1980

Further information by:

Organizing Committee
7th World Congress of Anaesthesiologists
c/o Hamburg Messe and Congress GmbH
—Dept. for Congress Organisation—
P.O. Box 30 23 60. D-2000 Hamburg 36
Federal Republic of Germany

fentanyl

narcotic reversal pure and simple

Respiratory depression from fentanyl or other narcotic analgesics used in intravenous anaesthesia can rapidly be reversed by naloxone. This pure narcotic antagonist does not itself depress respiration or augment depression from non-narcotic sources. As Narcan Neonatal, naloxone is also the narcotic antagonist of choice for reversing neonatal depression from pethidine given to the mother during labour.

Narcan regd.
(naloxone)
Pure narcotic antagonist

Narcan is a registered trade mark. Full information available from your hospital pharmacist or on request from Winthrop Laboratories, Surbiton-upon-Thames, Surrey. **WINTHROP**

GUIDE TO CONTRIBUTORS

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. Two issues each year deal mainly with material of postgraduate educational value.

PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publishers.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted.

LEGAL CONSIDERATIONS

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

PREPARATION OF MANUSCRIPT

Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full addresses) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

Title page

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should also be suggested.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the experiments to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of experimental results, while concise, should permit repetition of the experiments by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of

The choice is yours with the

PORTEX EPIDURAL SYSTEM

The most advanced design of Epidural Cannula* - smooth, flexible, kink-resistant, with excellent flow rates.

The Epidural Minipack - complete with the Portex Epidural Cannula** and thin-wall, single-use Tuohy needle - safe and economical with no costly extras.

The Portex Epidural Filter to complete the system, offering an effective bacterial and particulate barrier.

* Cannula supplied sterile in 16G and 18G, in radio-opaque or clear nylon. Option of 16G clear Cannula with open end.

** Minipack supplied sterile in 16G and 18G. Choice of radio-opaque or clear nylon Cannula.

For further details contact:

PORTEX LIMITED,
HYTHE, KENT, ENGLAND, CT21 6JL.
Tel: 66863 / 60551 Telex 96165

PORTEX S.A.,
ZI. de la VIGOGNE
62600 BERCK-SUR-MER,
FRANCE. Tel: (21) 090582

PORTEX

digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

Discussion

The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially.

References

There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

In the case of books, the reference should be as follows: name of author and initials; year of publication in parentheses; title of book, underlined; number of edition; page number; town of origin, publisher; for example: Hill, D. W. (1971). *Physics Applied to Anaesthesia*, 2nd edn, p. 212. London: Butterworths.

The *British Journal of Anaesthesia* should be referred to as *Br. J. Anaesth.*

In the text up to three authors should be named before the use of "... et al.". If reference is made to several publications during a particular year, written by a larger group of authors who have alternated the order of authorship, as many names must be written as are necessary to distinguish between the publications, before use of "... et al." in conjunction with the year suffixes a, b, c.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase "(in press)" replacing volume and page number.

It is essential that authors verify the content and details of references which they list, as this responsibility cannot be accepted by either Editors or Publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ ◐
◑ ◒ ⦿ ⊙ ⦶ ⊕ ⊖ ▩ ■ ▤ × +

The name of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It is emphasized that care taken in the original preparation of figures will obviate the time-consuming and expensive necessity of their revision.

EAST OF OXFORD

...is a name known throughout the world for advanced and reliable electro-mechanical anaesthetic apparatus.

The East-Radcliffe Mk. 5 Ventilator

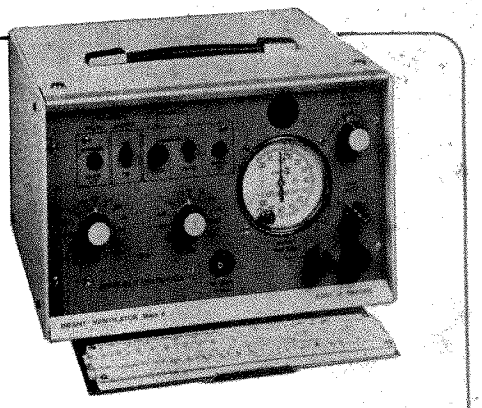
The latest model in a well-proven series – reliable and simple to operate. Autoclavable patient circuitry. Variable respiration rate. The unit may be used as a time-cycled pressure generator or as a volume-limited ventilator.

Hyperthermia Unit

This controlled water temperature unit will supply warm or cool water to a blanket within the 4°C to 40°C range. Readily portable, quiet, corrosion proof and reliable.

Humidifier Unit

East's blower-assisted humidifier unit provides a steady stream of warm, saturated air or oxygen for spontaneously breathing patients using tracheostomy boxes.



Sheffield Infant Ventilator Mk. 4

For anaesthesia or long-term ventilation of infants up to the age of three, the Mk. 4 unit is time-cycled, volume-controlled and pressure-limited with a wide range of respiratory rates.

East-Freeman Ventilator

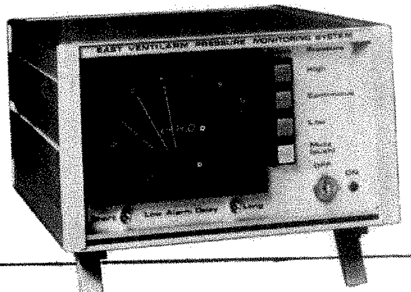
Suitable for long or short-term use in ward or intensive care units – or in the operating theatre for controlled/assisted ventilation with anaesthetic gases

East-Radcliffe Respirator

A highly compact theatre trolley unit which can supply anaesthetic gases by hand or automatically. The unit will also function as a ward ventilator.

The East Ventilarm Pressure Monitor/Alarm System

The East Ventilarm provides maximum protection to a patient connected to a lung ventilator and is activated by any change in the pressure pattern.



H.G. EAST & COMPANY LTD.

Littlemore, Oxford. OX4 5JT. Tel: Oxford 779361

A subsidiary of British Syphon Industries Ltd.

General information

Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available:

1.	PART I	(capitals)
2.	RESULTS	(small capitals)
3.	Blood-gas analysis	(l.c. roman)
4.	*The action of drugs*	(italics, centre)
5.	*Lung function studies*	(italics, full out)
6.	*Volume.* Large volumes. . . .	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet "Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors" (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

CORRESPONDENCE

It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

PROOFS

These should be corrected and returned to the sub-editor *within 48 hours of receipt.* Overseas contributors should return their proofs by airmail.

REPRINTS

Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

TECHNICON™ BG II™

pH/Blood Gas System

microprocessor controlled,
fully automatic,
self-calibrating, with
simplicity of operation.

The Technicon BG II represents the highest state of the art in automated blood gas analyzers.

Automated analysis: calibration, microprocessor monitoring of performance,compensation for barometric pressure, patient haemoglobin and temperature, printout of results. "Works-in-a-drawer" convenience and accessability. And eleven results — the most complete grouping of test parameters by any blood gas instrument.

. . . backed by Technicon Total Systems Support

Technicon Instruments Company Limited
Evans House, Hamilton Close,
Basingstoke, Hants. RG21 2YE
Telephone: Basingstoke (0256) 29181

You've worked hard for your money

-now let it work hard for you.

Like you, we at Lombard rely on our hard earned skills. Our experience over many years has made us an important name in British Banking and Finance to help people like you make their money grow by depositing with us.

We have a wide range of specially designed Deposit Account Schemes offering sound rates of interest which is paid without deduction of tax at source.

For further details of our deposit facilities and current interest rates without any obligation, simply post the coupon today.

Lombard North Central
Bankers

To:
LOMBARD NORTH CENTRAL LTD,
DEPT. U942,
17 BRUTON STREET,
LONDON W1A 3DH.
Tel: 491 7050

Name:
(BLOCK CAPITALS PLEASE)
Address:

A member of the National Westminster Bank Group whose capital and reserves exceed £1,300,000,000.

ANESTHESIOLOGY REVIEW contributes to the continued clinical education of anesthesia practitioners.

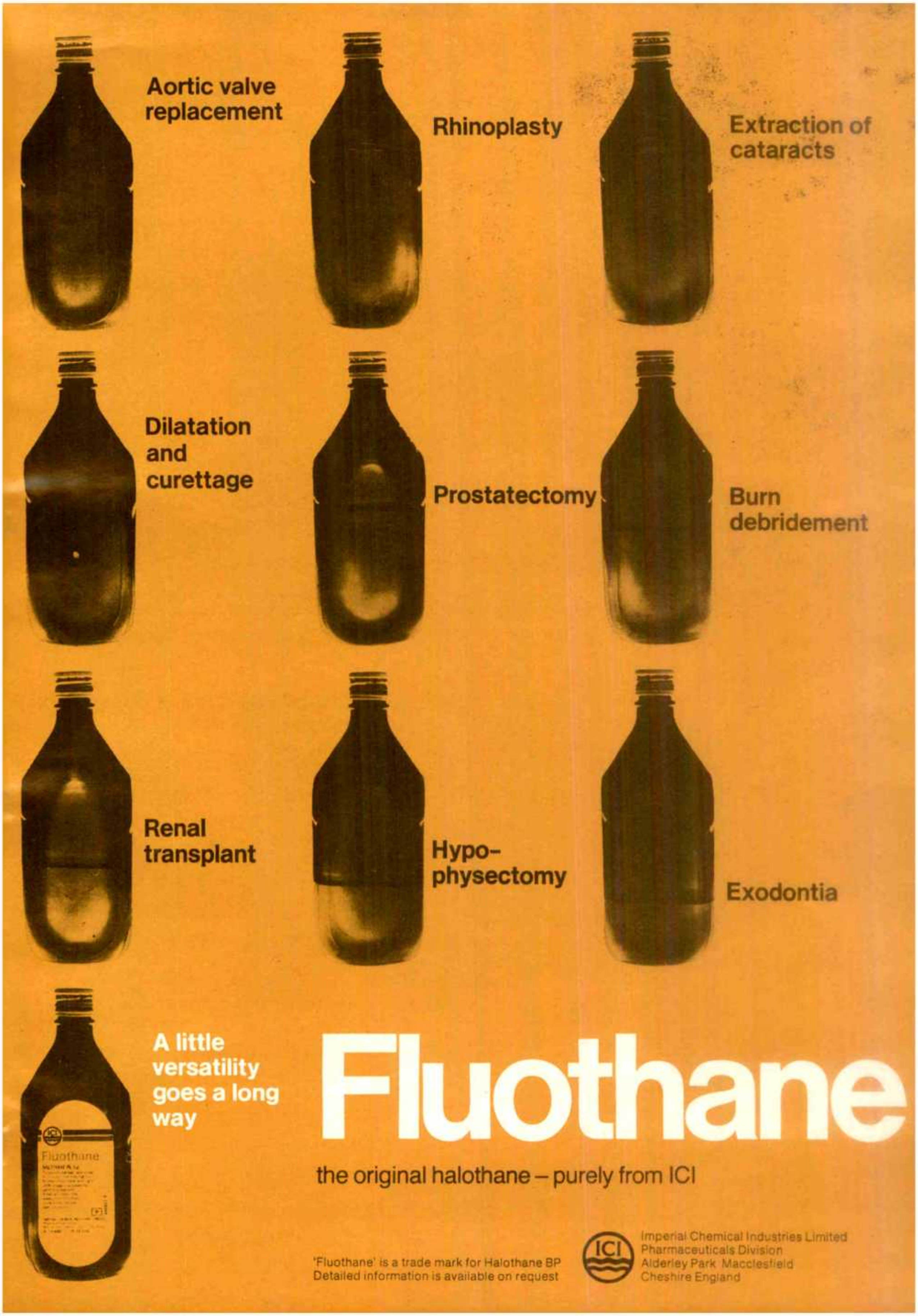
ANESTHESIOLOGY REVIEW, published monthly, presents original articles, current information on important clinical developments, case reports, symposia, book reviews, and abstracts from the world's literature.

ANESTHESIOLOGY REVIEW helps anesthesiologists in their day-to-day practice.

Subscription, $32.50 p.a. Foreign, $25.00 p.a. United States.
Send orders to:

ANESTHESIOLOGY REVIEW
275 Madison Avenue
New York, N.Y. 10016 U.S.A.

Anesthesiology Review
VOLUME I
NUMBER I
February
For Continuing Education in Clinical Anesthesiology
"And the Lord God caused a deep sleep to fall upon Adam, and he slept."



'Fluothane' is a trade mark for Halothane BP
Detailed information is available on request

ICI
Imperial Chemical Industries Limited
Pharmaceuticals Division
Alderley Park Macclesfield
Cheshire England

Der *Anaesthesist*

The organ of the
Austrian, German and Swiss Societies
of Anaesthesiology and Reanimation

Edited by: A. Doenicke, München; R. Frey, Mainz; O. Mayrhofer, Wein; H. Schaer, Männedorf
Managing Editor: A. Doenicke, München, Chirurgische Universitäts-Poliklivik, Anaesthesie, Pettenkoferstr. 8a, D-8000, München 2

Contents	OCTOBER 1979	
H. Steinhoff, K. Strasser, R. Heuler	Regurgitation and aspiration of gastric juice during delivery. Aetiology, prophylaxis and treatment	463
J. Tarnow, W. Hess	Flunitrazepam-pretreatment for preventation of adverse cardiovascular effects following Ketamine	468
V. O. Lang	H.R.P.-system 2000. A new universally applicable ventilation system for single or limited multiple use with high bacteriologic-hygienical safety	474
N. Franke, P. Schmucker, K. van Ackern, E. Kreuzer, B. Reichart	Control of afterload by intravenous nitroglycerin in patients undergoing myocardial revascularisation	484
W. Abbushi, E. Kolb, G. Herkt, J. Zenker	Clinical and experimental investigations concerning to positioning of head injured patients	489
R. Larsen, L. Drobnik, J. Teichmann, J. Radke, D. Kettler	The effects of halothane-, nitroprusside- and trimethaphan-induced hypotension on cerebral blood flow and intracranial pressure	494
E. Voigt	Material changes of plastic syringes	497

Annual subscription: DM 180 + postage

Published by SPRINGER-VERLAG · Berlin · Heidelberg · New York

---

COMPUTERS IN CRITICAL CARE AND PULMONARY MEDICINE

June 3–6, 1980

The second symposium will be held at the University of Lund, Lund, Sweden, with the purpose of exchanging information about computer applications and new technology.

Contributors are asked to register early. Abstracts and suggestions are welcome at any time. Detailed information will be distributed at a later date.

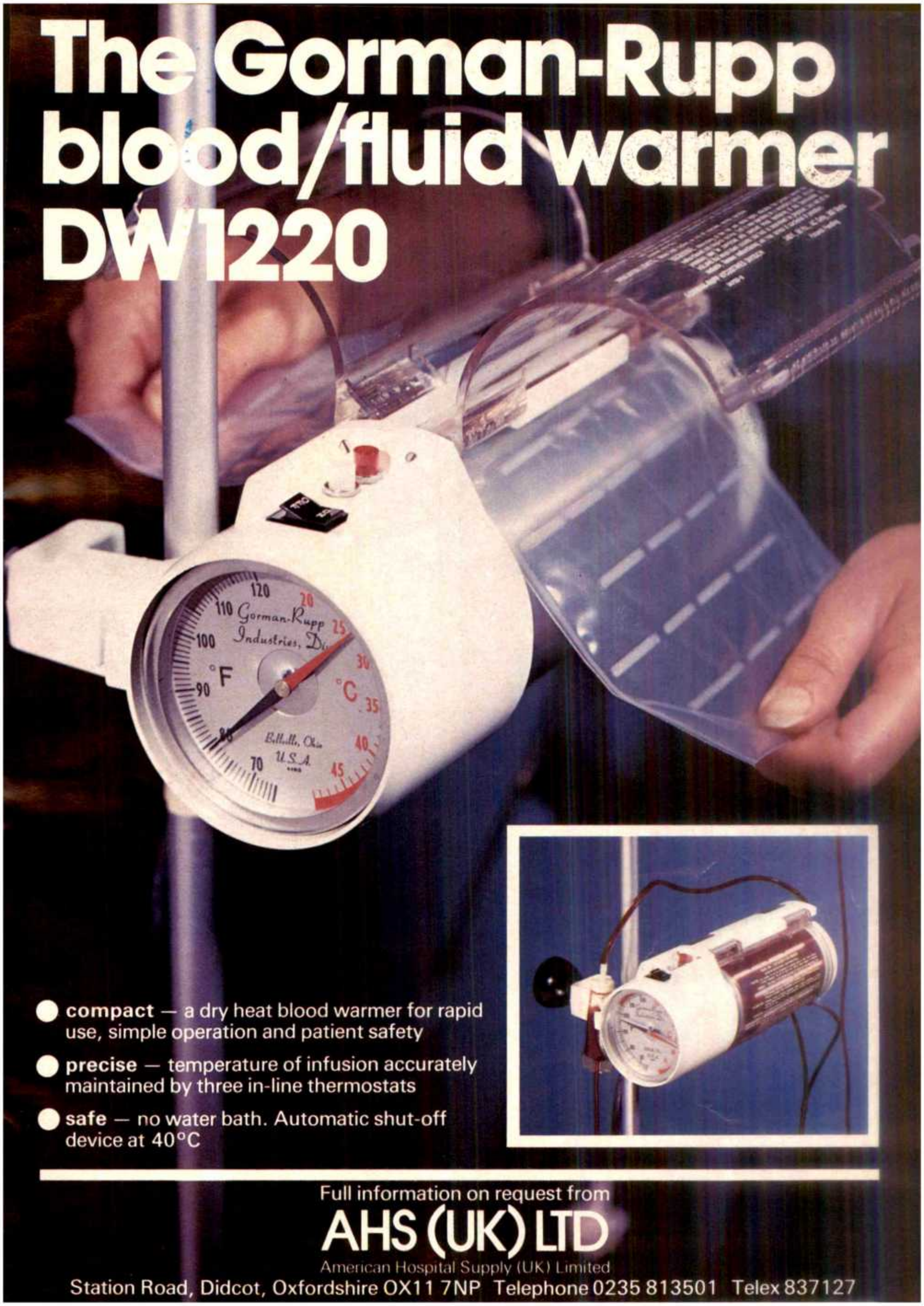
The following is a list of tentative topics:

- Lung physiology and pathophysiology
- The clinical pulmonary function laboratory
- Ventilation/perfusion relationships in cardiovascular disease and IPPV
- Monitoring and data acquisition
- Measurements of FRC, lung water, and perfusion in the ICU or operating room
- Mathematical models and simulation

Correspondence regarding abstracts, papers, registration and symposium accommodation to:

Miss Bodil Richardson,
Symposium Secretary,
Kliniskt Fysiologiska Avdelningen,
(Department of Clinical Physiology),
Lasarettet,
S-221 85 Lund,
Sweden.

The Gorman-Rupp blood/fluid warmer DW1220



- **compact** — a dry heat blood warmer for rapid use, simple operation and patient safety
- **precise** — temperature of infusion accurately maintained by three in-line thermostats
- **safe** — no water bath. Automatic shut-off device at 40°C

Full information on request from

AHS (UK) LTD

American Hospital Supply (UK) Limited
Station Road, Didcot, Oxfordshire OX11 7NP Telephone 0235 813501 Telex 837127

INTERNATIONAL CONGRESS ON DEATH AND DYING

March 31–April 2, 1980

The Congress will be held at Imperial College, London SW1.

Further details from:
The Conference Office,
37a, Maida Vale,
London W9.

ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN AND IRELAND
AND
SOCIETY OF ANAESTHETIC LABORATORY TECHNICIANS

A Joint Scientific Meeting will be held at New Hall College, Cambridge, on Friday and Saturday, March 28–29, 1980.

Further details are available from:
Mrs A. M. Rhodes,
Division of Anaesthesia,
Clinical Research Centre,
Watford Road,
Harrow,
Middlesex HA1 3UJ. Telephone: 01-864 5311, extn 2163.

This Handbook is an essential reference for anaesthetists and those associated with the speciality.

Designed to provide factual and commercial information of value to departments of Anaesthesia in their dealings with other organisations and to those wishing to commence the practice of anaesthesia as a training.

Handbook of British Anaesthesia 1979/80

Contents include comprehensive information on:
National and International bodies in Anaesthesia
National specialist societies
Regional and local societies
University departments of anaesthesia
National Health Service Postgraduate Training areas and National Health Service Advisory and Consultative machinery

Published price of the Handbook is £5.95 but there is a special price to subscribers of the journal. For information write to:
Sally Pimley, Macmillan Journals Limited, 4 Little Essex Street,
London WC2R 3LF, England.

6TH ASIAN AND AUSTRALASIAN CONGRESS OF ANAESTHESIOLOGISTS

Auckland, New Zealand, January 19–22, 1982

Information can be obtained from:

The Convenor,
6th Asian and Australasian Congress of Anaesthesiologists
Department of Anaesthesia,
Auckland Public Hospital,
Auckland,
New Zealand.

THE FIRST SAN ANTONIO—UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER

SYMPOSIUM ON NEUROANESTHESIA

April 12–14, 1980

The symposium will be held at the Four Seasons-Plaza Nacional Hotel in downtown San Antonio, Texas. The major theme will be Neurosciences and Neuroanaesthesia.

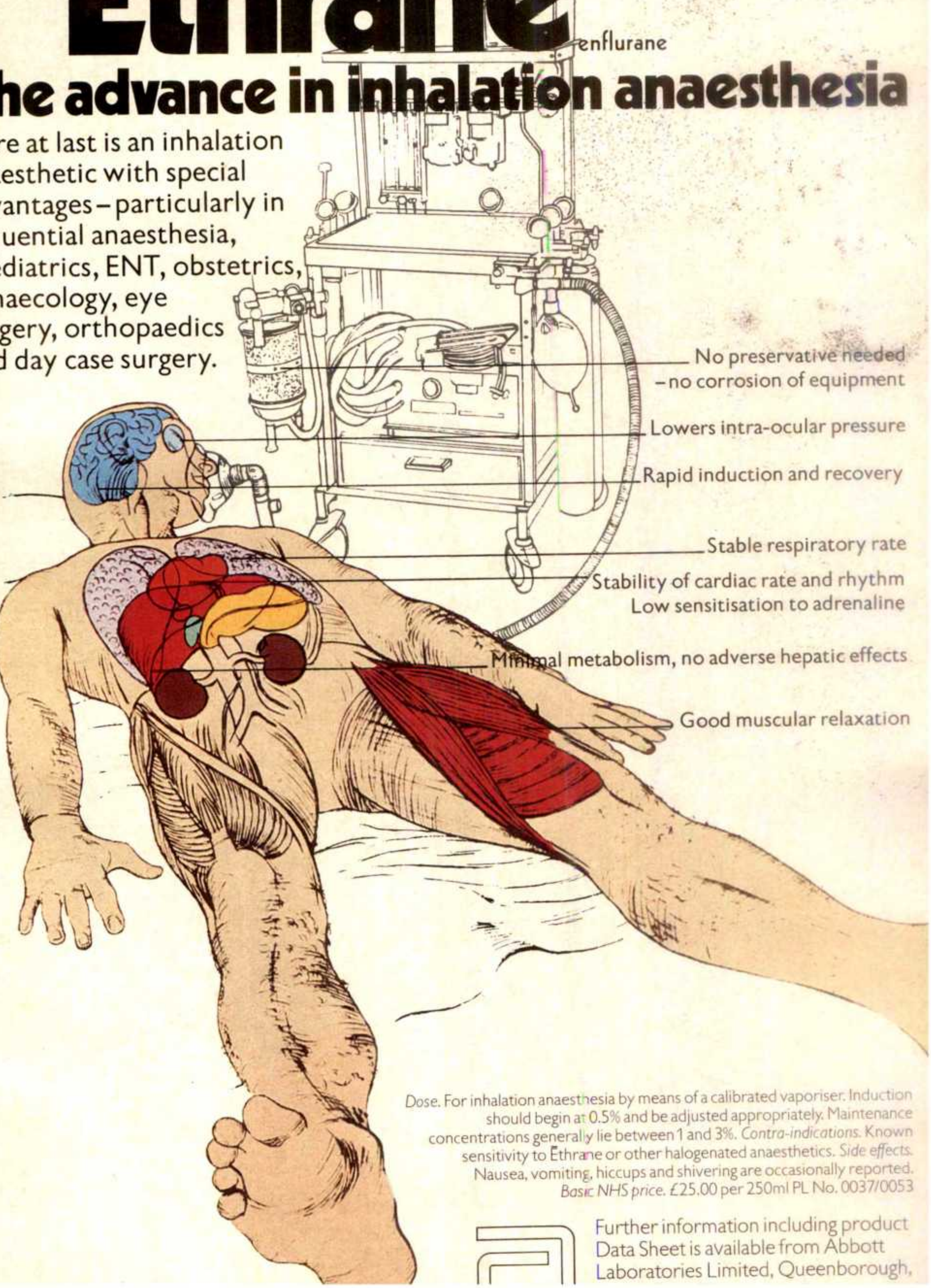
Further information:

Maurice S. Albin, M.D., M.SC. (ANES.),
Department of Anesthesiology,
The University of Texas Health Science Center,
7703 Floyd Curl Drive,
San Antonio, Texas 78284, U.S.A.

Ethrane® enflurane

The advance in inhalation anaesthesia

Here at last is an inhalation anaesthetic with special advantages – particularly in sequential anaesthesia, paediatrics, ENT, obstetrics, gynaecology, eye surgery, orthopaedics and day case surgery.


No preservative needed – no corrosion of equipment
Lowers intra-ocular pressure
Rapid induction and recovery
Stable respiratory rate
Stability of cardiac rate and rhythm
Low sensitisation to adrenaline
Minimal metabolism, no adverse hepatic effects
Good muscular relaxation

Dose. For inhalation anaesthesia by means of a calibrated vaporiser. Induction should begin at 0.5% and be adjusted appropriately. Maintenance concentrations generally lie between 1 and 3%. *Contra-indications*. Known sensitivity to Ethrane or other halogenated anaesthetics. *Side effects*. Nausea, vomiting, hiccups and shivering are occasionally reported. *Basic NHS price*. £25.00 per 250ml PL No. 0037/0053

Further information including product Data Sheet is available from Abbott Laboratories Limited, Queenborough,

BRITISH MEDICAL BULLETIN

Each Issue a Symposium on an Important Aspect of Contemporary Medical Research

VOL. 36, NO. 1 **JANUARY 1980**

CHEMICAL CARCINOGENESIS

Scientific Editor: *P. Brookes*

Introduction	*P. Brookes*
The history and future of chemical carcinogenesis	*E. Boyland*
The metabolic activation of chemical carcinogens	*Peter Sims*
DNA as a target of alkylating carcinogens	*P. D. Lawley*
Cellular responses to carcinogen-induced DNA damage and the role of DNA repair	*J. J. Roberts*
In-vivo–in-vitro analysis of ethylnitrosourea-induced brain carcinogenesis in the rat	*Joan P. Roscoe*
Multistage carcinogenesis in the urinary bladder	*R. M. Hicks*
Carcinogenesis by fungal products	*R. C. Garner*
Carcinogenesis and mineral fibres	*J. C. Wagner, G. Berry and F. D. Pooley*
Bacterial mutation as an indicator of carcinogenicity	*S. Venitt*
Carcinogenic synergism and its reflection *in vitro*	*John Ashby and J. A. Styles*
Interactions between carcinogens and proteins	*B. Ketterer*
Bracken fern and papilloma virus in bovine alimentary cancer	*W. F. H. Jarrett*
Antigenic changes in chemical carcinogenesis	*M. J. Embleton and R. W. Baldwin*
Bacterial metabolism and human carcinogenesis	*M. J. Hill*
Chemical carcinogenesis: whither epidemiology?	*Michael Alderson*

Price: UK, £6·00; Other countries, £7·20; USA and Canada, $15.00

Order from your local bookseller, or direct from

BRITISH MEDICAL BULLETIN
65 DAVIES STREET, LONDON W1Y 2AA

CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

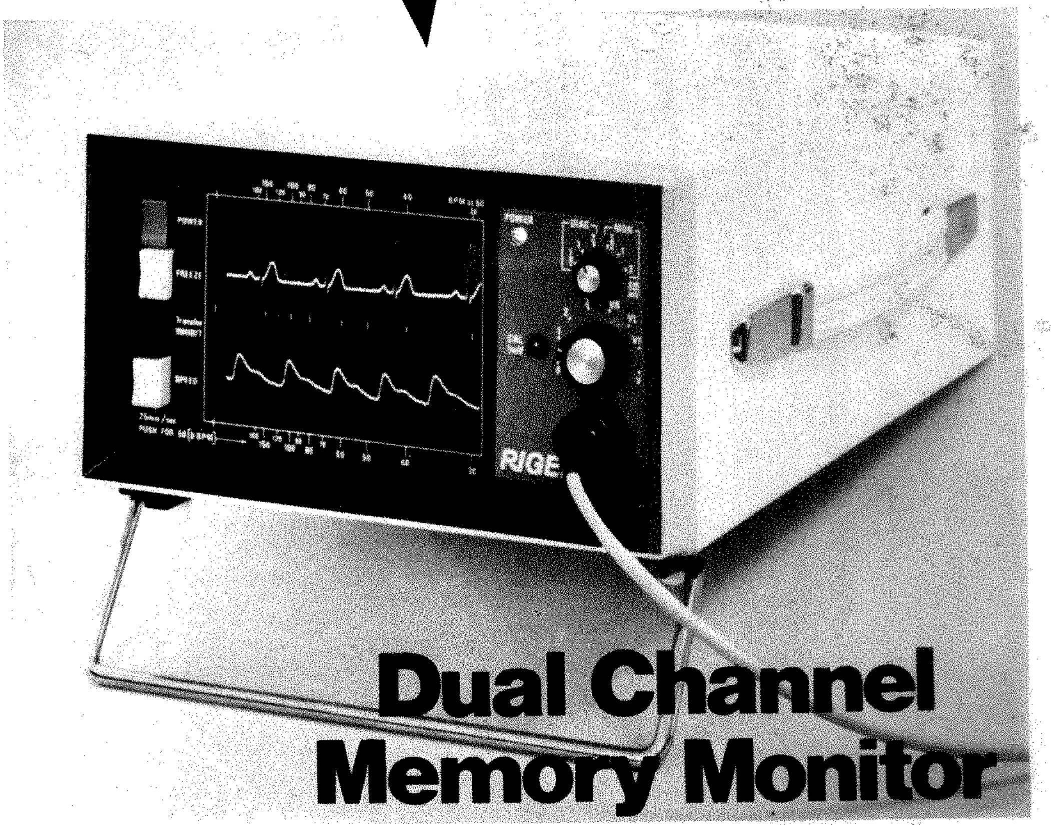
Editor
R. A. GORDON
Assistant Editor: GORDON WYANT
Editorial Board
MARCEL BOULANGER A. W. CONN DOUGLAS B. CRAIG
KENNETH M. LEIGHTON EMERSON MOFFITT R. A. MELOCHE BERNARD PAIEMENT

The Journal is issued bi-monthly for members of the Society and Subscribers. It contains original articles and reviews on clinical and basic science subjects related to Anaesthesia.

Annual Subscription $30.00 post paid

First Class Airmail $12.00 extra (optional).

The Secretary
Canadian Anaesthetists' Society
178 St. George Street, Toronto M5R 2M7, Ontario, Canada



PATIENT MONITORING SYSTEMS RIGEL

Dual Channel Memory Monitor

Model DM813

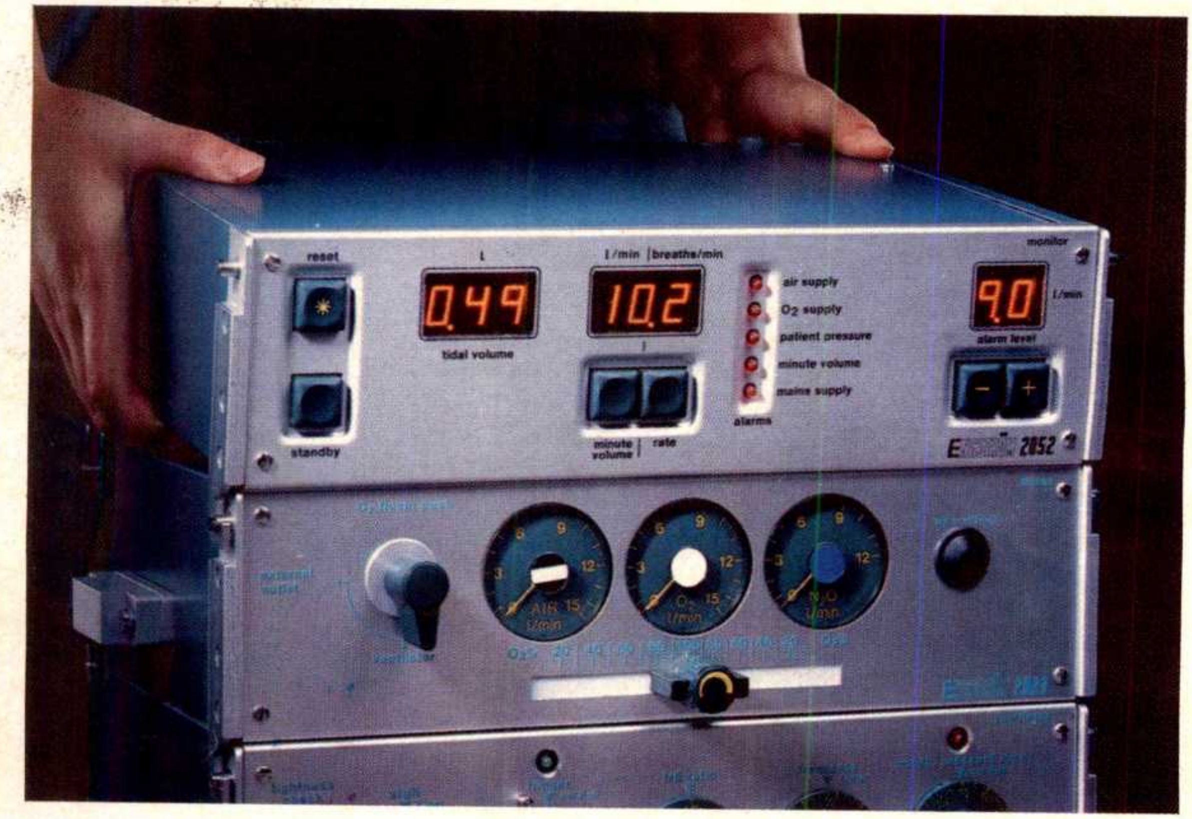
Special features include

Clear non-fade Display ● ECG & Pulse Wave or ECG with Cascade Channel ● Compact and Portable Design ● Patient Lead Switching ● Earth-free Patient Circuits ● Heart Rate Scale on Screen ● Freeze & Dump Facilities ●

For further information telephone or write to:
RIGEL RESEARCH LTD., 99 Gander Green Lane, Sutton, Surrey.
Telephone 01-642 2288/9

The Engström 2000 respirator with a brand new monitoring unit.

It can even print what's happening.



A new microprocessor controlled monitoring unit for the ventilation of the patient gives individual and easily-identified alarms that cover all situations. It gives you a digital display of breath-to-breath tidal volumes, true minute volumes, and the spontaneous or manual breathing rate.

The Engström 2000 is an electronic, modular design. It gives stable settings and has a wide choice of programmed functions, including PEEP, Trigger, Sigh, spontaneous breathing and manual ventilation.

A special feature is the printer output. A standard printer can give you a continuous printout of respiratory parameters and alarm conditions, if they occur. This printout, in plain words, is a unique Engström feature.

Your nearest Engström representative will be glad to give more information, or to arrange a demonstration.

ENGSTRÖM

Engström Medical AB,
Box 1295, S-171 25 Solna, Sweden

Engström 2000 - the respirator with features that puts it ahead of all others.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 1 JANUARY 1980

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement.

EDITORIAL

MATERNAL MORTALITY AND ANAESTHESIA

The Report on Confidential Enquiries into Maternal Deaths in England and Wales 1973–75 (Department of Health and Social Security, 1979) and the report on an Enquiry into Maternal Deaths in Scotland 1972–75 (Scottish Home and Health Department, 1978) contain much information of concern to anaesthetists. Regional assessors have evaluated the contribution of anaesthesia to individual maternal deaths and it is probable that an accurate assessment of this contribution has been made in most cases, although incomplete information hindered assessment in a few. These reports are examples of "peer review" on a national scale which are of great potential value.

In the periods covered by the reports, 13.2% of 220 true maternal deaths in England and Wales (E. and W.) and 14% of 50 true maternal deaths in Scotland were attributed to anaesthesia. In E. and W. the number of maternal deaths from all causes decreased by 36% since the preceding triennium, but the number of deaths resulting from anaesthesia decreased only from 37 to 31 with the result that the mortality rate as a result of anaesthesia increased from 10.4% to 13.2%. Avoidable factors were present in 90% of deaths attributable to anaesthesia in E. and W. and in Scotland an avoidable factor existed in every case. In Scotland all seven deaths were associated with general anaesthesia. In E. and W. two deaths were caused by extradural analgesia and 29 by general anaesthesia. General anaesthesia was an important factor in a further six deaths in E. and W.

General anaesthesia caused 21% of deaths associated with Caesarean section in E. and W. and 38% in Scotland. Caesarean section is increasingly used to solve obstetric problems and is often performed in the interest of the fetus, yet anaesthesia can threaten the survival of mother and infant. Even elective Caesarean section is not without risk. Anaesthesia resulted in the death of five mothers undergoing elective section. The fatality rate for Caesarean section was about 1 in 1250 operations (E. and W.) to 1 in 2000 operations (Scotland) and the risk of death from anaesthesia was about 1 in 6000 operations (E. and W.) to 1 in 7500 (Scotland).

More than 70% of deaths were associated with emergency surgery, but it is disturbing to note that anaesthesia for sterilization in the puerperium caused four deaths and two women died from anaesthesia administered for termination of pregnancy. General anaesthesia for emergency Caesarean section caused 14 of 21 deaths in E. and W. and three of seven deaths in Scotland. There was a total of five deaths from general anaesthesia for forceps delivery and it is regrettable that regional analgesia has not entirely replaced general anaesthesia in all centres. There is a welcome trend towards extradural analgesia for Caesarean section (Moir, 1979).

For the first time since 1955, abortion was not the commonest cause of maternal death in E. and W. The mortality rate from amniotic fluid embolism was unchanged at 7% and the death rate from pulmonary thromboembolism was unaltered. Haemorrhage caused 10% of all deaths (less than anaesthesia) and in half of these cases a serious coagulation defect had developed. Cerebral haemorrhage remained the principal cause of death in hypertensive states. The number of deaths from heart disease had decreased by half since 1970–73 in E. and W.

Obstetric anaesthesia was sometimes given by inexperienced anaesthetists with fatal consequences. The assessors rightly regard this as the result of an organizational failure and such administrative failure caused 12 deaths (30% of deaths as a result of anaesthesia) in E. and W. For example, a senior house officer anaesthetized a patient with severe haemorrhagic shock; he had no opportunity for assessment before surgery. The patient was asthmatic and developed severe bronchospasm on intubation. There was delay with blood for tranfusion; hypoxia and hypoyolaemia caused fatal cardiac arrest. Anaesthetic, surgical and administrative deficiencies produced this result. The patient's life may well depend upon the actions of the anaesthetist and it is the view of the Obstetric Anaesthetists Association that obstetric anaesthesia should not be given by an unsupervised anaesthetist with less than 1 year's experience. Consultant help, where available, may arrive too late. There is a need for more consultant anaesthetists with a special interest in obstetric anaesthesia and analgesia to teach safe techniques and to organize obstetric anaesthesia services. The problem of the small, isolated obstetric unit is almost insoluble and closure may be indicated (Hunter and Moir, 1979).

Detailed consideration of these maternal deaths seems to call for reappraisal of some aspects of the preparation for anaesthesia and the technique of induction of anaesthesia. Pulmonary aspiration of stomach contents killed 13 mothers in E. and W. and three in Scotland. Eleven of these 16 women died of Mendelson's syndrome, yet nine were reported to have received oral alkali during labour and before anaesthesia. Crucial information as to the volume, frequency of administration and nature of the alkali is not supplied, but eight of the nine women who died of Mendelson's syndrome in E. and W. had received "the recommended dosage of antacids" and "adequate antacid therapy". Alkalis are not invariably or equally effective and dosage is important (Peskett, 1973; Holdsworth, 1978). In the absence of fuller information it can be concluded that (a) the alkali therapy was not "adequate", (b) in a minority of cases alkalis are ineffective in the "recommended dosage" or (c) the aspiration of acid is not the sole cause of Mendelson's syndrome. The now classic study of Taylor and Pryse-Davies (1966) involved the use of gastric aspirates containing food particle in addition to hydrochloric acid. There is the intriguing possibility that particles of magnesium trisilicate might be a pulmonary irritant. Prophylactic alkalis should be given, but further information about optimal dosage and perhaps the choice of alkali is needed. There may prove to be a role for cimetidine to prevent further acid secretion in labour.

Measures to reduce the possibility of regurgitation and aspiration should be used, although no single measure ensures safety. Gastric intubation or i.v. apomorphine have a role in high risk cases. Cricoid pressure should always be used and in the correct manner. In five cases cricoid pressure was incorrectly applied and in seven cases it was not used, with fatal consequences. Skilled assistance should be available to the anaesthetist.

Failure to intubate the trachea resulted in death on seven occasions in E. and W. and four occasions in Scotland. In some of the cases the tube was known or suspected to have been in the oesophagus. Persistent attempts at intubation are rarely successful and may lead only to hypoxia or regurgitation. Anaesthetists should carry out a failed intubation drill (Tunstall, 1976) and be prepared to continue anaesthesia with a volatile or gaseous agent, spontaneous ventilation and a face-mask. Hypoxia develops with abnormal rapidity in pregnancy (Archer and Marx, 1974) and pre-oxygenation is essential.

Misuse of drugs because of ignorance of basic pharmacology caused four deaths in E. and W. On two occasions bradycardia as a result of suxamethonium given without atropine proved fatal. There were two deaths because of accidents with apparatus, one from disconnection of the ventilator and one from emptying of the oxygen cylinder.

For the first time there were two deaths from continuous lumbar extradural analgesia in labour. Both were judged to have been a result of accidental subarachnoid injection and there was failure to observe the patients and to institute proper treatment. A trained anaesthetist must be immediately available when extradural analgesia is used.

It is the right of every pregnant woman and unborn child to receive the highest standard of anaesthesia and analgesia at all times. It is the duty of every department of anaesthesia to fulfil this obligation. In the long term additional consultant anaesthetists will be required, but meanwhile much could be achieved by reviewing priorities and redeploying existing staff. It is the duty of the department to ensure that there is adequate, functioning equipment and skilled assistance for the anaesthetist in the obstetric unit.

Donald D. Moir

REFERENCES

Archer, G. W., and Marx, G. F. (1974). Arterial oxygen tension during apnoea in parturient women. *Br. J. Anaesth.*, **46**, 358.

Department of Health and Social Security (1979). Report on Confidential Enquiries into Maternal Deaths in England and Wales 1973–1975. London: H.M. Stationery Office.

Holdsworth, J. D. (1978). A fresh look at magnesium trisilicate. *J. Int. Med, Res.*, **6**, (Suppl. 1), 70.

Hunter, A. R., and Moir, D. D. (1979). Maternity services and the anaesthetist. *Br. J. Anaesth.*, **51**, 169.

Moir, D. D. (1979). Extradural analgesia for Caesarean section. *Br. J. Anaesth.*, **51**, 79.

Peskett, W. G. H. (1973). Antacids before obstetric anaesthesia. A clinical evaluation of the effectiveness of mist. magnesium trisilicate BPC. *Anaesthesia*, **28**, 509.

Scottish Home and Health Department (1978). A Report on an Enquiry into Maternal Deaths in Scotland 1972–1975. Edinburgh: H.M. Stationery Office.

Taylor, G., and Pryse-Davies, J. (1966). Prophylactic use of antacids in the prevention of the acid-pulmonary-aspiration syndrome (Mendelson's syndrome). *Lancet*, **1**, 288.

Tunstall, M. E. (1976). Failed intubation drill. *Anaesthesia*, **31**, 850.

Br. J. Anaesth. (1980), 52, 5

DYNAMIC BEHAVIOUR OF THE CHEST AND OF THE ABDOMEN IN ANAESTHETIZED PIGLETS DURING RAPID INSUFFLATION

M. ARBORELIUS JR AND S. LINDAHL

SUMMARY

Three piglets were ventilated with a TVM-ventilator, which releases predetermined volumes of compressed gas into the airways. The inspiratory flow depends on the pressure and volume of the compressed gas and compliance, resistance and inertia of the lungs, thorax and abdomen of the subject. The time for half filling of the chest was less than that of the abdomen and the difference increased with high driving pressure (with high acceleration). The difference was thus most probably a result of greater inertia of the abdomen. Inertia also seemed to influence the emptying of the lungs. This was so slow that increase of FRC—air trapping—was seen at a ventilatory frequency of 30 b.p.m. The practical consequences of these findings are that the abdomen (diaphragm) will take less and less part in ventilation and that a phase lag between chest and abdominal breathing should become larger with increasing ventilatory frequency. FRC will increase in regions with expiratory obstruction and lung rupture may follow.

The partition of gas between various lung regions has been shown to be governed by airway resistance and compliance of the lung, rib cage and of the abdomen (Konno and Mead, 1967; Grimby, Hedenstierna and Löfström, 1975). A thorough discussion of these factors has been given by Sybrecht and others (1976) who, in contradiction to Robertson, Anthonisen and Ross (1969), concluded that neither airway resistance nor compliance could explain why relatively less gas went to diaphragmatic lung regions during rapid as compared with slow inhalations in the supine position. A difference in intrapleural pressure was considered to be the only remaining factor that could explain the phenomenon during spontaneous breathing. Such a pressure difference must be a result of phase lag between thoracic muscles and diaphragm. A phase lag between thoracic and abdominal breathing movements at increasing ventilatory frequency has also been noted recently by Faithfull, Jones and Jordan (1979).

The purpose of this study was to observe time constants for the movement of chest and abdomen using rapid inflation of gas in animals in which complete neuromuscular block had been induced.

MATERIALS AND METHODS

Three piglets of the Swedish native breed were investigated in 12 experiments. Piglet I (weight 12 kg) took part in experiments 1, 2, 7 and 8, piglet II (7 kg) in experiments 3, 4, 9 and 10 and piglet III (8 kg) in experiments 5, 6, 11 and 12 (table I).

A combination of droperidol (Dridol) 1–2 mg kg^{-1} and ketamine (Ketalar) 30–50 mg kg^{-1} injected i.m. was used for anaesthesia. Alcuronium (Alloferin) 1–2 mg was given i.v. when necessary for the maintenance of neuromuscular block.

The piglets were studied in the supine position and the trachea intubated with a cuffed orotracheal tube (Portex no. 5), connected to a Tidal Volume Monitoring ventilator (TVM-ventilator) (Lindahl and Okmian, 1979) and the lungs ventilated with air.

The TVM-ventilator (fig. 1A) was used for artificial ventilation, as it allows independent changes in driving pressure, tidal volume and ventilatory frequency. The ventilator consists of rigid chambers in which the breathing gas is compressed. When opening the inspiratory valve, air flows into the airways and lungs until a pressure equilibrium between the chamber and the airways and lungs is reached. The pressure difference $P_1 - P_2$ (fig. 1B) is adiabatic and proportional to a certain amount of gas, which depends upon the volume of the pressure chamber. In this apparatus the pressure chambers had volumes rendering compliances (C_{vent} ml kPa^{-1}) of 20, 40 and 80 ml kPa^{-1}. The tidal volume (V_{T} ml) is accurately

---

MÅNS ARBORELIUS, JR, M.D., PH.D., Department of Clinical Physiology, University of Lund, Malmö General Hospital, S-214 01 Malmö, Sweden. STEN LINDAHL, M.D., PH.D., Department of Anaesthesia, University of Lund, University Hospital, S-221 85 Lund, Sweden.

0007-0912/80/01005-06 $01.00

© Macmillan Journals Ltd 1980

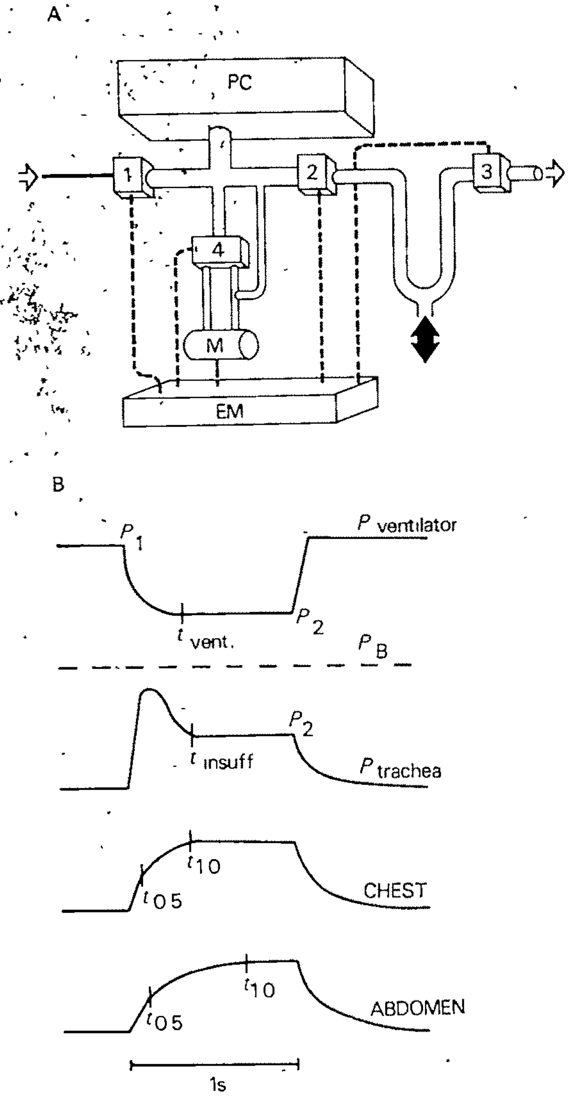


FIG. 1. A. The ventilator: 1 = filling valve; 2 = inspiratory valve; 3 = expiratory valve; 4 = differential pressure valve; M = differential manometer; PC = pressure chamber; EM = electronic module for synchronization of the valve function. Open arrows denote gas inlet and outlet. Filled arrow the tracheal connection. B. Pressure curves (P_{vent} and $P_{trachea}$) and volume changes in per cent of full inspiration of the chest and of the abdomen. Measured times (t_{vent}, t_{insuff}, $t_{1.5}$ and $t_{1.0}$ see text) are indicated. P_1 = initial pre-inspiratory pressure in the ventilator pressure chamber. P_2 = end-inspiratory pressure, which is identical in the trachea and in the ventilatory pressure chamber. P_B = atmospheric pressure.

determined breath-by-breath (Lindahl, 1977). With this type of ventilator the ventilatory frequency can be varied without any change in driving pressure during inspiration (P_{vent}), end-inspiratory tracheal pressure ($P_{trachea}$) and magnitude of tidal volume. This principle offers several advantages which cannot be achieved with earlier known ventilators and was a prerequisite for this investigation.

Different ventilatory settings were used (table I) and an unchanged alveolar ventilation ($P\text{A}_{CO_2}$) was controlled by an end-tidal sampler synchronized with the ventilator's working cycle and connected to an infra-red carbon dioxide analyser (Godart, Holland).

Frequent arterial samples were withdrawn and blood-gases analysed by conventional methods (Instrumentation Laboratories 213, Boston, USA). The correlation between end-tidal P_{CO_2} and Pa_{CO_2} was satisfactory ($r = 0.80$) in these piglets with healthy lungs. No significant changes in Pa_{O_2} occurred.

Tracheal pressures and pressures in the ventilator's pressure chamber were measured with electromanometers (Siemens–Elema, EMT 34).

Two mercury silastic tube strain gauges were used, one in the middle of the sternum and the other 5 cm distal to the xiphoid process. The generated resistance changes from these two strain gauges were recorded with the tracheal and ventilator pressures on an ink-jet recorder (Siemens–Elema, EMT 81). Changes in resistance were proportional to the volume changes in the chest and in the abdomen and were linear within the measuring range. The volume changes were expressed as a percentage of the end-inspiratory volume, since absolute volume calibration for each strain gauge was both difficult to achieve and unnecessary for the purpose of the study. Five to 10 deflections were recorded, but no measurable differences occurred between the cycles.

The time needed to reach a terminated deflection of insufflation ($t_{1.0}$) from each strain gauge was measured. In the same way the time needed to reach half this amplitude ($t_{0.5}$) was measured. In all but experiment no. 7, end-inspiratory plateaux were reached, that is no change in volume or pressure was recorded. The insufflation time (t_{insuff}) (at static end-inspiratory pressure in the trachea) and the time needed to reach static end-inspiratory pressure in the ventilator pressure chamber (t_{vent}) were measured also (fig. 1).

All records were obtained 15 min after the setting of an adequate ventilation.

TABLE I. *C_{vent} = ventilator volume/pressure quotient; f = ventilatory frequency; P_{vent} = pre-inspiratory pressure in the ventilator pressure chamber; P_{peak} = greatest tracheal pressure; P_{el} = end-inspiratory tracheal pressure; V_T = tidal volume; t_{vent} = time needed for a terminated pressure change in the pressure chamber; t_{insuff} = the time needed for reaching end-expiratory pressure in the trachea; $t_{0.5}$ and $t_{1.0}$ = time for 50% and 100% filling of chest and abdomen during inspiration*

		Ventilator setting												
		C_{vent}		Insp. time	P_{vent}	P_{peak}	P_{el}	V_T	t_{vent}	t_{insuff}	$t_{0.5}$(s)		$t_{1.0}$(s)	
Piglet	Expt	(ml kPa^{-1})	f	(s)	(kPa)	(kPa)	(kPa)	(ml)	(s)	(s)	Chest	Abdomen	Chest	Abdomen
I	1	40	10	1.2	8.7	3.2	2.2	260	0.36	0.42	0.05	0.13	0.32	1.14
	2	40	30	1.0	4.7	1.9	1.2	140	0.32	0.32	0.04	0.10	0.28	0.90
II	3	40	10	1.2	6.1	3.4	2.1	160	0.41	0.46	0.10	0 13	0.60	0 70
	4	40	30	1.0	2.9	2.1	0.9	80	0.31	0.35	0.06	0.13	0.30	0.95
III	5	40	10	1.2	5.8	3.4	1.5	170	0.38	0.44	0.11	0.12	0.58	0.66
	6	40	30	1.0	2.5	1.6	0.7	70	0.30	0.36	0.08	0.08	0.30	0.37
I	7	40	20	0.3	6.6	2.2	2.1	180	0.30	0.30	0.07	0.11	0.29	0.29
	8	40	20	1.0	6.3	2.6	1.8	180	0.38	0.40	0.07	0.11	0.33	1.0
II	9	20	20	1.0	6.7	4.0	1.2	110	0.31	0.38	0.04	0.10	0.30	0.33
	10	80	20	1.0	2.6	2.1	1.2	110	0.45	0.50	0.07	0.16	0.35	0.98
III	11	20	20	1.0	7.0	3.0	1.0	120	0.26	0.31	0.03	0.05	0.33	0.31
	12	80	20	1.0	2.5	1.6	1.0	120	0.35	0.41	0.11	0.11	0.40	0.82
								Mean	0.34	0.39	0.07	0.11	0.37	0.70
								SD	0.05	0.06	0.03	0.03	0.11	0.31
											$P < 0.001$		$P < 0.01$	

Current statistical methods for mean values and SD were used. Paired significance tests (Student's *t* test) were applied.

RESULTS

The results are presented in table I. With the exception of experiments 6 and 12, $t_{0.5}$ was shorter for the chest than for the abdomen (fig. 2). Experiments 6 and 12 were characterized by a low driving pressure (P_{vent}) and relatively small tidal volumes (low accelerative forces during inspiration). The difference in $t_{0.5}$ for the chest *v.* the abdomen was statistically significant ($P < 0.001$).

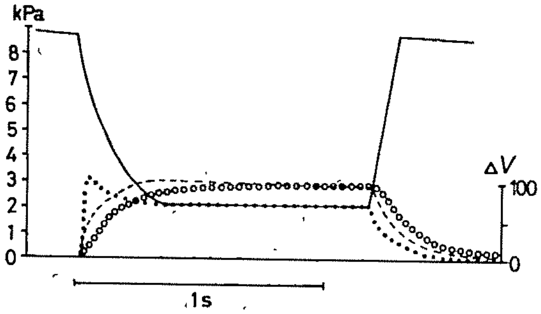


FIG. 2. Tracings from experiment 1. P_{vent} (——), $P_{trachea}$ (....) and volume changes of the chest (------) and of the abdomen (O O O O O). Note time differences in both inspiratory and expiratory volume changes of the chest and of the abdomen.

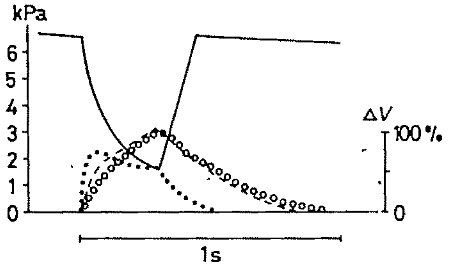


FIG. 3. Tracings from experiment 7. The same plan as figure 2. Note that the inspiration is terminated at the same time in both chest and abdomen. Expiratory volume changes are identical during the first part of expiration.

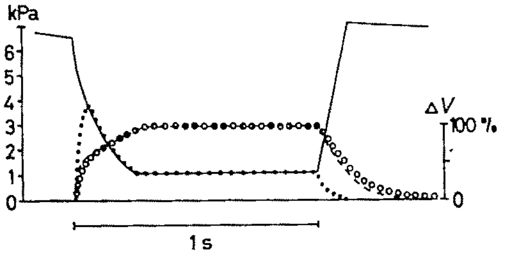


FIG. 4. Tracings from experiment 11. The same plan as figures 2 and 3. Note the correspondence between volume changes of the chest and of the abdomen when high initial driving pressures were used but the delivered volume was small. $t_{0.5\ chest}$ was, however, only 50% of $t_{0.5\ abd}$, even if both were so brief that the visual difference was small.

The differences appeared to be greatest in experiments with high driving pressures (high accelerative forces during inspiration (nos 1, 9 and 11)). In most measurements $t_{1.0}$ was less for the chest than for the abdomen ($P < 0.01$). An exception was in experiment 7, where inspiration was interrupted before the end-inspiratory volume was reached (fig. 3). A high driving pressure and moderate tidal volumes (9 and 11) resulted in an equal $t_{1.0}$ (fig. 4).

It was found that the volume change of the chest structures ($t_{1.0\,\text{chest}}$) followed the evacuation of the pressure chamber (t_{vent}) closely, while the volume change of the abdomen ($t_{1.0\,\text{abd}}$) lagged considerably in most cases (fig. 5A, B; table I). This was most obvious in experiments with high driving pressure and large tidal volumes.

It was found also that the expiratory flow was mainly affected by distention of the lung and was more rapid in early expiration at larger tidal volumes (i.e. directly proportional to the distending pressure). Furthermore, it was faster for the chest than for the abdomen (fig. 2). This difference seemed to be less pronounced when the structures were not expanded to their normal compliance at the commencement of exhalation (fig. 3). It was possible to demonstrate a substantial increase in the end-expiratory volume (air-trapping) (fig. 6A, B) even in these healthy piglets when expiration time was too short ($f = 30$ b.p.m. and 50% expiration time).

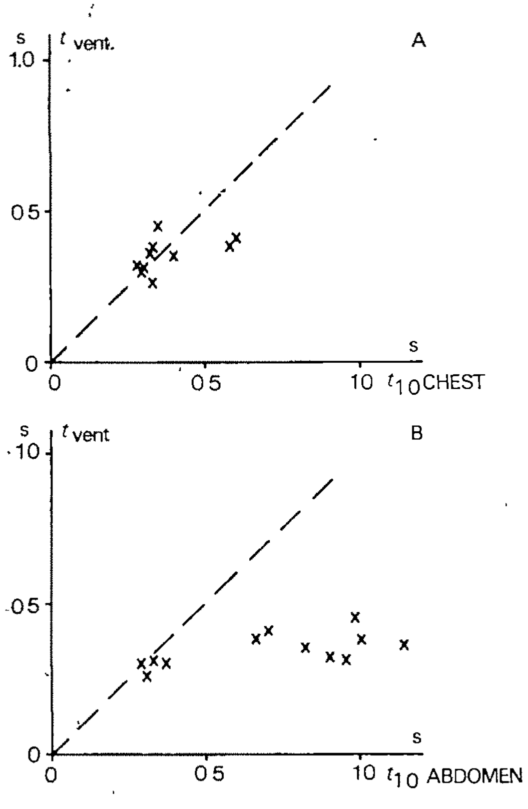


FIG. 5. t_{vent} plotted against time for complete filling of the chest (A) and abdomen (B). Dashed lines = lines of identity. Note that filling of the abdomen continues in most cases when no driving pressure exists in the ventilator—redistribution of gas from chest to abdomen must take place.

DISCUSSION

Sybrecht and others (1976) found that the basal parts of the lungs received less of an inhaled gas bolus with increasing speed of voluntary inhalation in supine man. They showed that different resistances in bronchi to apical and diaphragmatic areas could not explain their results. Faithfull, Jones and Jordan (1979) showed that a phase lag between thoracic and abdominal breathing movements occurred with increasing frequency of breathing as registered with strain gauges over the thorax and abdomen. The results of both these studies might be explained by slower or weaker muscle response of the diaphragm/abdomen compared with the intercostals.

In the present experiments all muscles were relaxed. Nevertheless, the chest filled more rapidly than the abdomen, a difference that was more pronounced with rapid insufflation. According to the calculations of Sybrecht and others (1976), different resistances in airways to areas of lung associated with movement of the diaphragm/abdomen and the chest is an unlikely explanation of the phenomenon. Furthermore, the thoracic volume change in our study was recorded over the middle part of the sternum. Therefore airways leading to lung regions expanding ventrally (chest) and caudally (abdomen) must, to some extent, be the same, which make flow-dependent differences in airway resistance an improbable explanation for the differences in time constants. The only remaining cause for the different pattern of movement of chest and abdomen during muscle relaxation is differences in inertia.

If the chest of the piglets is considered as a cylinder with a diameter and length of 10 cm and if it should increase its volume by 200 ml, there would be a change in diameter of about 0.6 cm. If the diaphragm, considered as a piston, should perform the same volume change it must move 2.6 cm. The acceleration of the abdomen would thus be approximately five times greater than that of the chest wall. The chest wall moves in air, while the diaphragm must

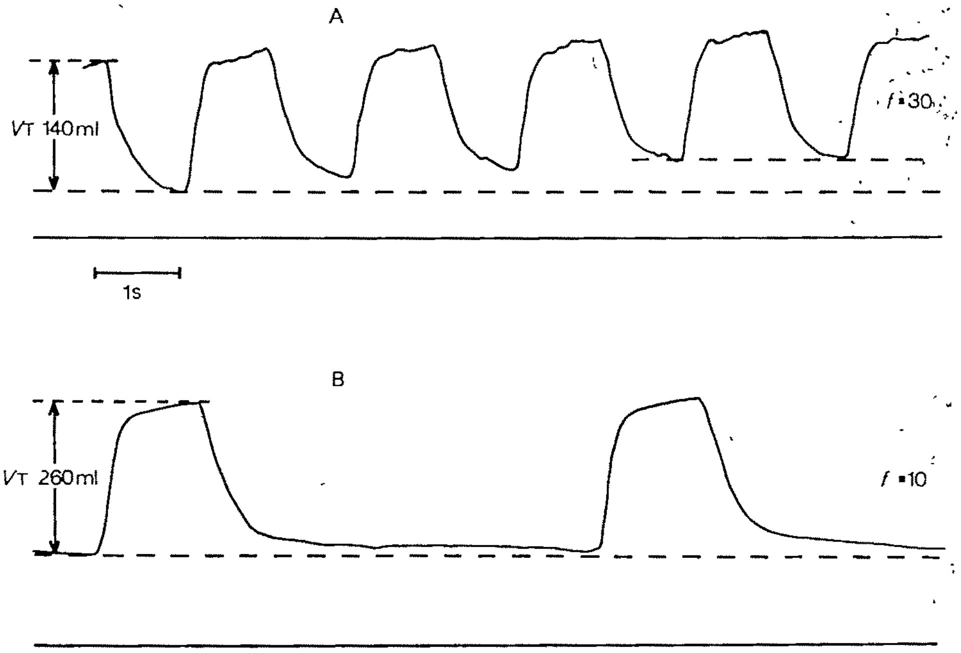


FIG. 6. Volume tracings from experiment 1 at a ventilatory frequency of 30 b.p.m. (A) and of 10 b.p.m. (B). Note that the end-expiratory volume increases during the first part of ventilation at the greater frequency.

displace water. The high inertia of the diaphragm/abdomen will counteract acceleration during the first phase of inflation and retardation during the later phase. This explains the difference in movements of the chest and abdomen shown in figure 3 and causes a small redistribution of gas at the end of inspiration, demonstrated in figure 5A and B. High inertia of the abdomen in relation to the chest, acting both during inhalation and exhalation, could easily explain the increasing phase shift at greater breathing frequencies found by Faithfull, Jones and Jordan (1979).

In our healthy piglets, using normal sizes of tracheal tube and low expiratory resistance of the circuit, the time needed for a complete expiration was so long that the normal end-expiratory level was not reached at a ventilatory frequency of 30 b.p.m. with an expiration time 50% of the whole breathing cycle. During the first ventilatory cycles FRC increased by more than 30 ml (fig. 6A, B) with a tidal volume of 140 ml. With a tidal volume of 260 ml at a ventilatory frequency of 10 b.p.m. and an expiration time of 80% of the breathing cycle FRC did not change. In obstructive lung disease expiratory time constants increase more than inspiratory time constants. High inspiratory pressures maintained throughout the inspiration will cause hyperinflation of lung regions with long expiratory time constants (Lindahl, Arborelius and Okmian, 1979) eventually leading to lung rupture (Kirkpatrick, Felman and Eitzman, 1974; Berg et al., 1975; Ogata et al., 1976) unless long expiration times are used.

With increasing ventilatory frequency the diaphragmatic parts of the lung will take a decreasing part in ventilation and with very high ventilatory frequencies (Jonzon et al., 1971) mainly chest wall ventilation is to be expected.

ACKNOWLEDGEMENTS

This investigation was supported by grants from the Swedish Medical Research Council, Project no. B76-17X-4519-02.

REFERENCES

Berg, T. J., Pagtakhan, M. H., Reed, C. L., and Chernick, V. (1975). Bronchopulmonary dysplasia and lung rupture in hyaline membrane disease: Influence of continuous distending pressure. *Pediatrics*, **55**, 51.

Faithfull, D., Jones, J. G., and Jordan, C. (1979). Measurement of the relative contribution of rib cage and abdomen/diaphragm to tidal breathing in man. *Br. J. Anaesth.*, **51**, 391.

Grimby, G., Hedenstierna, G., and Löfström, B. (1975). Chest wall mechanics during artificial ventilation. *J. Appl. Physiol.*, **38**, 576.

Jonzon, A., Öberg, Å., Sedin, G., and Sjostrand, U. (1971). High-frequency positive pressure ventilation by endotracheal insufflation. *Acta Anaesthesiol. Scand.* (Suppl.) 43, 24.

Kirkpatrick, B. V., Felman, A. H., and Eitzman, D. V. (1974). Complications of ventilatory therapy in respiratory distress syndrome. Recognition and management of acute air leaks. *Am. J. Dis. Child.*, **128**, 496.

Konno, K., and Mead, J. (1967). Measurement of separate volume changes of rib cage and abdomen during breathing. *J. Appl. Physiol.*, **22**, 407.

Lindahl, S. (1977). Experimental and clinical studies on volume-controlled artificial ventilation in young individuals. Thesis, University of Lund, Sweden.

—— Arborelius, M., jr, and Okmian, L. (1979). Influence of ventilatory frequencies and ventilator volume/pressure quotients on pulmonary ventilation using a tidal volume ventilator. *Acta Anaesthesiol. Scand.*, **23**, 379.

—— Okmian, L. (1979). Experimental studies on artificial ventilation using a tidal volume ventilator. Mechanics and dynamics of ventilation. *Acta Anaesthesiol. Scand.*, **23**, 359.

Ogata, E. S., Gregory, G. A., Kitterman, J. A., Phibbs, R. H., and Tooley, W. H. (1976). Pneumothorax in the respiratory distress syndrome: Incidence and effect on vital signs, blood-gases and pH. *Paediatrics*, **58**, 177.

Robertson, P. C., Anthonisen, N. R., and Ross, D. (1969). Effect of inspiratory flow rate on regional distribution of inspired gas. *J. Appl. Physiol.*, **26**, 438.

Sybrecht, G., Landau, L., Murphy, B. G., Engel, L. A., Martin, R. R., and Maclem, P. T. (1976). Influence of posture on flow dependence of distribution of inhaled Xe^{133} boli. *J. Appl. Physiol.*, **41**, 489.

COMPORTEMENT DYNAMIQUE DE LA POITRINE ET DE L'ABDOMEN DE PORCELETS ANESTHESIES PENDANT UNE INSUFFLATION RAPIDE

RESUME

Trois porcelets ont été ventilés à l'aide d'un ventilateur TVM, lequel relâche des volumes prédéterminés de gaz comprimé dans les passages d'air. Le débit inspiratoire dépend de la pression et du volume du gaz comprimé, de même que de la compliance, de la résistance et de l'inertie des poumons, du thorax et de l'abdomen du sujet. Le temps nécessaire pour remplir la poitrine à moitié a été inférieur à celui qu'il a fallu pour l'abdomen et la différence s'est élargie lorsque la pression d'entraînement a été augmentée (avec une haute accélération). La différence a donc très probablement été le résultat d'une plus grande inertie de l'abdomen. L'inertie a aussi semblé influencer le vidage des poumons. Cela a été si lent que l'augmentation de la FRC—rétention d'air—a été vue à une fréquence ventilatoire de 30 respirations mn^{-1}. La conséquence pratique de ces découvertes est que l'abdomen (diaphragme) prendra de moins en moins part à la ventilation et que le déphasage entre la respiration de la pointrine et la respiration abdominale deviendra plus important avec l'augmentation de la fréquence ventilatoire. La FRC augmentera dans les régions où il y a une obstruction respiratoire et il peut s'ensuivre une rupture des poumons.

DYNAMISCHES VERHALTEN VON BRUTS UND UNTERLEIB BEI NARKOTISIERTEN FERKELN WÄHREND SCHNELLER INSUFFLATION

ZUSAMMENFASSUNG

Drei Ferkel wurden mit einem TVM-Ventilator beluftet, der vorbestimmte Mengen komprimierten Gases in die Luftwege leitete. Der Einatmungsfluss hing von Druck und Volumen des komprimierten Gases, sowie von Dehnbarkeit, Widerstand und Trägheit von Lunge, Brustkorb und Unterleib des Tieres ab. Die Zeit für die halbe Fullung des Brustraumes war geringer als fur den Unterleib, und dieser Unterschied wurde grosser bei höherem Antriebsdruck (bei mehr beschleunigter Fullung). Der Unterschied war also wahrscheinlich Resultat der grosseren Tragheit des Unterleibes. Tragheit schien auch das Entleeren der Lungen zu bestimmen, das so langsam war, dass ein Anstieg von FRC—funktionelle Residualkapazitat oder Luftreste—bei einer Belüftungsfrequenz von 30 b.p.m. zu sehen war. Die praktische Folge dieser Resultate ist, dass der Unterleib (Zwerchfell) weniger und weniger an der Beluftung teilnimmt, und dass der Phasenabstand zwishen Brustraum—und Unterleibsatmung bei steigender Beluftungsfrequenz grosser wird. FRC wird in Regionen mit Ausatmungshindernissen ansteigen, was zu Lungenriss fuhren kann.

COMPORTAMIENTO DINAMICO DEL PECHO Y DEL ABDOMEN DE CHANCHITOS DURANTE INSUFLACION RAPIDA

SUMARIO

Mediante un ventilador-TVM, se ventiló a tres chanchitos al soltar volúmenes predeterminados de gases comprimidos en las vías respiratorias. El flujo inspiratorio depende de la presión y del volumen del gas comprimido y de la reacción, resistencia e inercia de los pulmones, del tórax y del abdomen del sujeto. La duración para llenar a medias el pecho fue inferior a la del abdomen y la diferencia aumentó cuando la presión de compresión era alta (con alta acceleración). La diferencia fue por consiguiente el resultado de una mayor inercia del abdomen probablemente. La inercia pareció influir también en el vaciamiento de los pulmones. Fue tan lento que ocurrió un aumento del FRC—retención del aire—en una frecuencia de ventilación de 30 b.p.m. La consecuencia práctica de estos resultados indican que el abdomen (diafragma) participará cada vez menos en la ventilación y que una brecha de la fase entre la respiración torácica y abdominal se volverá mayor con una creciente frecuencia de ventilación. El FRC aumentará en áreas con obstrucción expiratoria y puede acarrear una ruptura de los pulmones.

Br. J. Anaesth. (1980), **52**, 11

PORCINE MALIGNANT HYPERTHERMIA. VII: HEPATIC METABOLISM

G. M. HALL, J. N. LUCKE, R. LOVELL AND D. LISTER

SUMMARY

Hepatic metabolism during porcine malignant hyperthermia (MH) was investigated in seven Pietrain pigs. The estimated hepatic blood flow decreased during MH, but an increase in oxygen extraction enabled the splanchnic oxygen uptake to be maintained. There was a large release of glucose and potassium from the liver in MH which made an important contribution to the hyperglycaemia and hyperkalaemia. Measurement of hepatic uptake of the precursors of gluconeogenesis, lactate, glycerol and alanine, showed that glucose efflux from liver was derived mainly from glycogenolysis. Lactate uptake by the liver increased during MH, and there was no evidence of hepatic lactate production during the profound acidosis as suggested by *in vitro* studies with the isolated liver. There was no evidence of major abnormality of hepatic function during porcine MH.

Changes in circulating metabolites during porcine malignant hyperthermia (MH) have been described in detail (Berman et al., 1970; Jones et al, 1972; Lucke, Hall and Lister, 1976) and are considered to be secondary to the increased muscle metabolism, although the contribution of other organs and tissues cannot be discounted.

In this study with Pietrain pigs, we have examined liver function during the hyperthermic response to determine the contribution of liver metabolism to concentrations of substrates in the blood. In particular, the progressive lactic acidosis characteristic of MH may result from both increased anaerobic muscle metabolism and impaired lactate uptake by the liver. There is considerable evidence from *in vitro* studies of the liver that an acidic perfusate reduces lactate uptake and also causes hepatic lactate production (Hems et al., 1966; Lloyd et al., 1973; Iles et al., 1977). If this mechanism operates in porcine MH, it could be responsible for the fulminating nature of the acidosis.

METHODS

Animal preparation

Seven Pietrain pigs (mean weight 67 kg, SEM ± 5 kg) from the Meat Research Institute's herd were studied. On the day before the experiment the pigs were anaesthetized, using a technique described by Denny and Lucke (1977), for the insertion of a catheter to the hepatic vein. The right external jugular vein was catheterized with a 65-cm, 8-gauge "Cobra" angiographic catheter (Cordis, Ducor) which had the terminal 1.4 cm of the moulded curve removed. Under fluoroscopic control the catheter was passed across the right atrium, down the caudal vena cava and into a large right hepatic vein. The position of the catheter was checked by the injection of 10 ml of sodium iothalamate 70% (Conray 420) and the catheter filled with heparinized saline (1 mg ml^{-1}). The free end of the catheter was sutured securely at the site of the surgical incision. The procedure was completed within 40 min.

On the day of the experiment, anaesthesia was induced by injection of thiopentone 10–15 mg kg^{-1} through the hepatic venous catheter. After intubation of the trachea, the lungs were ventilated with 66% nitrous oxide in oxygen using a Cape–Waine ventilator and anaesthesia maintained with incremental doses of thiopentone. A 17-gauge Teflon cannula, 8 cm long (Dannula, I.C.I. Ltd), was placed in the left common carotid artery and a 61 cm, 14-gauge catheter (Bard I-Cath, C. R. Bard International Ltd), introduced via the left external jugular vein into the right atrium. The patency of the catheters was maintained by intermittent flushing with saline 0.9%. A thermocouple (ELLAB, Copenhagen) was placed 10 cm deep in the lateral aspect of the thigh muscle for measurement of muscle temperature.

G. M. HALL, M.B., B.S., PH.D., M.I.BIOL., F.F.A.R.C.S., Department of Anaesthetics, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS. J. N. LUCKE, B.V.SC., M.R.C.V.S., PH.D., D.V.A., Department of Veterinary Surgery, University of Bristol, Langford House, Langford, Bristol BS18 7DU. R. LOVELL, B.SC.; D. LISTER, B.SC., PH.D., F.I.BIOL.; ARC Meat Research Institute, Langford, Bristol BS18 7DY.

Correspondence to G. M. H.

0007-0912/80/010011-07 $01.00

© Macmillan Journals Ltd 1980

Experimental procedure

Liver blood flow was estimated by the continuous infusion of indocyanine green (ICG) (Bradley, 1962). Indocyanine green 10 mg was injected i.v. as a bolus and then the dye was administered as a continuous infusion at a rate of 0.5 mg min^{-1} into the right atrium using a calibrated infusion pump (C. F. Palmer Ltd). A constant arterial concentration of ICG was achieved after 20 min. Approximately 30 min after the start of infusion, control arterial and hepatic venous blood samples were collected simultaneously for the determination of pH, oxygen content, glucose, lactate, pyruvate, alanine, free fatty acids (FFA), glycerol, potassium and ICG values. In addition the arterial sample was analysed for the haematocrit, and concentrations of insulin and isocitrate dehydrogenase (ICDH). A second group of control samples was collected 10 min later. MH was then induced by ventilating the lungs with halothane 1% for 10 min and the administration of suxamethonium 1 mg kg^{-1} after 5 min ventilation with halothane. Paired arterial and hepatic venous samples were collected simultaneously every 10 min during MH until the pig died. These were analysed as described below.

Analyses

Blood pH was measured with a Radiometer blood-gas system (Radiometer Ltd, Copenhagen). The haematocrit was determined using a microcapillary haematocrit centrifuge with a correction for trapped plasma (Garby and Vuille, 1961). The oxygen content of the blood was measured directly in an electrolytic cell (Lex–O_2–Con, Lexington Instruments Corp.). The blood concentrations of glucose (Werner, Rey and Wielinger, 1970), lactate (Hohorst, 1962), pyruvate (Czok and Lamprecht, 1970) and alanine (Williamson, 1974) were determined enzymatically. Plasma was separated for the estimation of FFA (Duncombe, 1964), glycerol (Eggstein and Kuhlmann, 1974), ICDH (Wolfson, 1957) and potassium (atomic absorption spectrophotometry) concentrations. The plasma insulin concentration was determined using a solid-phase radioimmunoassay (Phadebas Insulin Test). Plasma ICG was measured spectrophotometrically at 805 nm (Rowell, 1974) and a calibration curve made for each pig with known dilutions of the dye used. All analyses were undertaken in duplicate except for the plasma insulin estimations, which were performed in triplicate.

The results are expressed as mean values ± SEM. Initially the data were analysed using a two-way analysis of variance (Armitage, 1971) to determine the presence of a significant change in mean concentration with time. Student's *t* test was applied to ascertain the degree of significance of this change during MH compared with the second control sample.

RESULTS

Arterial substrate and hormone concentrations (table I)

The arterial glucose concentration increased significantly during MH to a maximum value of 10.9 mmol litre^{-1} ($P<0.001$) after 20 min. The hyperglycaemia was associated with a small but significant increase in plasma insulin from 9.7 μu. ml^{-1} to 14.3 μu. ml^{-1} ($P<0.05$). The plasma potassium concentration increased rapidly from 4.0 mmol litre^{-1} in the control period to 7.1 mmol litre^{-1} after 10 min ($P<0.001$), but there was little further change with a concentration of 7.6 mmol litre^{-1} terminally ($P<0.001$). The significant increase in arterial lactate value during MH ($P<0.001$) was accompanied by a small increase in pyruvate concentration which became significant ($P<0.05$) only after 40 min.

There was a decrease in plasma FFA ($P<0.05$), but this was associated with an increase in glycerol value ($P<0.05$). The arterial alanine concentration increased progressively throughout the hyperthermic response, being 134 μmol litre^{-1} terminally ($P<0.001$).

Liver blood flow

The estimated hepatic blood flow (EHBF) (table II) decreased significantly from 1.10 litre min^{-1} in the control period to 0.42 litre min^{-1} after 10 min of halothane ($P<0.05$). The EHBF continued to decrease further with the development of MH to 0.27 litre min^{-1} after 40 min ($P<0.01$). The arterial oxygen content was well maintained during the hyperthermic response (12.6–14.8 ml dl^{-1}) and arterial–hepatic venous oxygen content difference increased significantly ($P<0.001$) so that there was only a small decrease in splanchnic oxygen uptake ($P<0.2$). The reduction in arterial pH and increases in muscle temperature and haematocrit, which are characteristic of MH, were significantly different from the control values after only 10 min ($P<0.001$). Arterial ICDH concentration increased from 1.5 u. litre^{-1} to 5.0 u. litre^{-1} ($P<0.01$) after 20 min and to 8.3 u. litre^{-1} ($P<0.001$) after 40 min.

Liver metabolism (table III)

The hepatic uptake or release of metabolites was calculated from the product of the difference between

TABLE I. *Mean (± SEM) arterial concentrations of metabolites and insulin during MH. n = number of pigs studied. Significance of difference of mean from −5 min shown by* *$P<0.05$, **$P<0.01$, ***$P<0.001$

		Control		Malignant hyperthermia			
	n	−15 min	−5 min	10 min	20 min	30 min	40 min
Glucose (mmol litre^{-1})	7	4.9±0.5	4.7±0.5	6.8±0.6*	10.9±1.6***	9.0±2.5**	8.1±0.8***
Potassium (mmol litre^{-1})	7	4.1±0.1	4.0±0.1	7.1±0.4***	7.1±0.4***	7.1±0.8***	7.6±0.7***
Lactate (mmol litre^{-1})	7	1.6±0.4	1.3±0.3	11.9±0.5***	17.9±1.6***	19.3±1.3***	19.3±0.9***
Pyruvate (μmol litre^{-1})	7	43±8	38±8	64±10	68±23	80±22	80±21*
Alanine (μmol litre^{-1})	7	71±17	65±14	86±7	108±8**	125±12***	134±9***
FFA (mmol litre^{-1})	7	0.39±0.04	0.41±0.05	0.27±0.04*	0.28±0.05*	0.29±0.07*	0.29±0.03*
Glycerol (mmol litre^{-1})	7	0.17±0.02	0.14±0.02	0.22±0.04*	0.29±0.06*	0.37±0.10*	0.27±0.07*
Insulin (μu. litre^{-1})	5	10.1±2.9	9.7±2.5	11.5±1.5	14.3±2.1*	12.1±0.9	12.0±0.5

TABLE II. *Mean (± SEM) values for hepatic physiology during MH. n = number of pigs studied. Significance of difference of means from −5 min shown by* *$P<0.05$, **$P<0.01$, ***$P<0.001$

		Control		Malignant hyperthermia			
	n	−15 min	−5 min	10 min	20 min	30 min	40 min
Arterial pH	7	7.45±0.01	7.44±0.03	7.10±0.03***	6.78±0.02***	6.74±0.03***	6.75±0.02***
Arterial O_2 content (ml dl^{-1})	5	14.3±0.6	15.0±0.5	14.6±0.3	12.6±0.6	12.9±0.8	14.8±0.8
Muscle temperature (°C)	7	37.9±0.5	37.8±0.5	38.9±0.2***	40.0±0.4***	40.9±0.4***	41.5±0.3***
Estimated hepatic blood flow (litre min^{-1})	7	0.97±0.13	1.10±0.18	0.42±0.07*	0.37±0.09**	0.29±0.03**	0.27±0.05**
($Ca_{O_2}-Chv_{O_2}$) content difference (ml dl^{-1})	5	5.5±0.3	6.2±0.3	12.6±0.7***	12.0±0.6***	12.8±0.8***	14.8±0.9***
Splanchnic O_2 uptake (ml min^{-1})	5	47±7	64±11	56±7	50±12	41±6	43±7
Haematocrit (%)	7	33.4±0.7	33.3±0.9	45.0±1.2***	47.1±1.6***	48.2±1.5***	49.3±1.4***
Isocitrate dehydrogenase (u. litre^{-1})	5	1.5±0.3	1.5±0.3	3.0±0.4	5.0±0.9**	6.0±2.1**	8.3±1.5**

TABLE III. *Mean (± SEM) hepatic exchange of metabolites during MH. Positive values indicate hepatic uptake and negative values indicate hepatic production. n = number of pigs studied. Significance of difference of means from −5 min shown by *P < 0.05, **P < 0.01, ***P < 0.001*

		Control		Malignant hyperthermia			
	n	−15 min	−5 min	10 min	20 min	30 min	40 min
Glucose (mmol min^{-1})	7	−0.36 ± 0.15	−0.57 ± 0.36	−2.20 ± 0.57*	−3.57 ± 1.15**	−1.85 ± 0.90	−0.80 ± 0.19
Potassium (mmol min^{-1})	7	−0.09 ± 0.05	−0.11 ± 0.04	−1.12 ± 0.21***	−0.19 ± 0.14	−0.04 ± 0.21	−0.09 ± 0.13
Lactate (mmol min^{-1})	7	0.19 ± 0.18	0.21 ± 0.08	1.19 ± 0.28**	0.93 ± 0.28*	0.59 ± 0.13*	0.57 ± 0.14*
Pyruvate (μmol min^{-1})	7	−4 ± 14	−6 ± 13	−60 ± 16*	−37 ± 11*	−14 ± 8	— —
Alanine (μmol min^{-1})	7	22 ± 6	18 ± 6	8 ± 2	1 ± 3*	9 ± 6	3 ± 3*
FFA (μmol min^{-1})	7	12 ± 22	50 ± 32	10 ± 8	4 ± 3	0 ± 8	5 ± 1
Glycerol (μmol min^{-1})	7	25 ± 8	21 ± 5	16 ± 6	11 ± 6	17 ± 11	12 ± 3

TABLE IV. *Mean rates of hepatic glucose production and the maximum theoretical contributions from lactate, glycerol and alanine uptake (expressed as glucose equivalents) during MH. †Expressed as glucose equivalents*

	Control	Malignant hyperthermia			
	−5 min	10 min	20 min	30 min	40 min
Glucose production (mmol min^{-1})	0.57	2.20	3.57	1.85	0.80
Glucose precursor uptake† (mmol min^{-1})					
Lactate	0.105	0.595	0.465	0.295	0.285
Glycerol	0.011	0.008	0.006	0.009	0.006
Alanine	0.009	0.004	0.001	0.005	0.002
Total precursor uptake (mmol min^{-1})	0.125	0.607	0.472	0.309	0.293
Glucose production derived from precursor substrate (%)	22	28	13	17	37

the arterial and hepatic venous concentrations of the metabolite and the liver blood flow or plasma flow as appropriate.

Hepatic glucose efflux increased significantly from 0.57 mmol min^{-1} in the control period to a maximum rate of 3.57 mmol min^{-1} after 20 min ($P < 0.01$). In association with the glucose efflux, pyruvate release increased significantly after 10 and 20 min ($P < 0.05$). There was a 10-fold increase in potassium efflux by the liver after 10 min ($P < 0.001$), but this returned to control values for the remainder of the hyperthermic response. Lactate uptake increased significantly to 1.19 mmol min^{-1} after 10 min ($P < 0.01$) and was still increased at 0.57 mmol min^{-1} terminally ($P < 0.05$). The uptake of alanine, FFA and glycerol decreased but this change was significant ($P < 0.05$) only for alanine after 20 and 40 min.

DISCUSSION

The EHBF decreased during porcine MH, but an increase in oxygen extraction enabled the splanchnic oxygen uptake to be maintained (table II). This homeostatic mechanism is also observed in severe muscular exercise (Wahren et al., 1971) and shows that the physiological response of the liver to MH was normal. Although the liver has an important role in determining circulating glucose, lactate and potassium concentrations in MH, there was no evidence of any major impairment of metabolic control (table III). Gronert and others (1978) have shown recently that myocardial metabolism was normal in hyperthermic Poland China pigs and it is probable that the primary cellular defect in porcine MH is confined to skeletal muscle.

"Steady-state" conditions are required when the Fick principle is applied to the measurement of tissue uptake or production of any substrate (Zierler, 1961). Kalant and colleagues (1978), for example, in their study of substrate utilization in the human forearm during exercise, maintained a constant arterial glucose and insulin concentration for 1 h before the experiment to permit accurate application of the Fick principle. The practical problems of achieving a "steady-state" are so great, however, that the classical metabolic studies of starvation (Owen et al., 1967), exercise (Ahlborg et al., 1974) and diabetes mellitus (Wahren et al., 1972) have failed to meet the strict criteria for use of the Fick principle. It is even more difficult in such a rapidly progressive metabolic disorder as MH and any small change in the calculated hepatic uptake or efflux of a metabolite is particularly hard to evaluate. Nevertheless, the changes in glucose and potassium release and lactate uptake observed during MH (table III) are so large that, in our opinion, they are unlikely to be invalidated by the lack of "steady-state" conditions.

There is good evidence from *in vitro* studies that severe acidosis decreases lactate uptake by the liver and may cause hepatic lactate efflux. On the other hand, the results of the few *in vivo* studies investigating the release of lactate by the liver during acidosis are conflicting (Cohen and Woods, 1976). Cohen and Iles (1977) considered that the problem would be resolved only by the careful measurement of lactate uptake across the liver of the intact animal during lactic acidosis. Our results fail to support the supposition that the liver may produce lactate in severely acidotic states (Lloyd et al., 1973). After 10 min of MH when the arterial pH was 7.10, lactate uptake was almost six times greater than the control value and was still three times greater after 40 min when arterial pH was 6.75 and EHBF reduced to 25% of control (tables II and III). Although hepatic lactate uptake was increased in MH the arterial lactate concentration continued to increase as a result of the gross stimulation of anaerobic muscle metabolism.

The major source of the arterial hyperglycaemia (table I) was hepatic glucose production (table III), but we have observed some glucose efflux from skeletal muscle (unpublished observations). The increase in hepatic glucose production was a result of both glycogenolysis and gluconeogenesis. It is possible to calculate the theoretical rate of gluconeogenesis from the rate of uptake of the precursors, lactate, alanine and glycerol, assuming maximum conversion efficiency (Wahren et al., 1971). The data show that during the control period approximately 22% of the glucose output was derived from gluconeogenic precursors (table IV). During MH the contribution from gluconeogenesis decreased to 13% and 17% after 20 and 30 min respectively before increasing to 37% terminally. An approximate calculation of the area under the hepatic glucose production curve shows that 70 mmol or 13 g of glucose was released during the hyperthermic response. About 9 g of glucose was produced by glycogenolysis and this correlates with the measured hepatic glycogen content of starved Pietrain pigs (glycogen 7.61 g kg^{-1} (as glucosyl units), liver weight 1.2 kg—Meat Research Institute's unpublished data). Thus the terminal stages of porcine MH are associated with total depletion of hepatic glycogen.

Hyperkalaemia is characteristic of porcine MH and is usually assumed to be derived from the increase in skeletal muscle metabolism. However, table III shows that there was a 10-fold increase in hepatic efflux of potassium after 10 min of MH. This returned rapidly to control values. The enhanced potassium production was not associated with the maximal rate of glucose production and the cause of this response is obscure. Gronert and Theye (1976) showed that there was little peripheral production of potassium during porcine MH and we conclude that the liver is the organ mainly responsible for the hyperkalaemia.

The significant decrease in arterial FFA values (table I) was noted in a previous study and interpreted as an inhibition of lipolysis (Lucke, Hall and Lister, 1976). The concomitant increase in glycerol concentration (table I) signifies an increase in lipolysis and the decline in FFA values must be a result of either re-esterification or increased uptake by tissues such as liver and muscle. Since there was no change in FFA uptake by either the liver (table III) or the muscle (unpublished observations), re-esterification is the most likely cause of the decrease in FFA values.

In conclusion, hepatic metabolism makes an important contribution to the changes in circulating lactate, glucose and potassium concentrations found in porcine MH. Hepatic glycogenolysis and potassium efflux are the main causes of the hyperglycaemia and hyperkalaemia of MH. The lacticacidaemia is a result of peripheral over-production with some impairment of lactate uptake but, in spite of the profound acidosis and hyperthermia, hepatic gluconeogenesis is never completely inhibited.

ACKNOWLEDGEMENTS

G. M. Hall received generous financial support from the Muscular Dystrophy Group of Great Britain. G. M. Hall and J. N. Lucke are visiting research workers at the ARC Meat Research Institute and thank Professor Norris for the use of the Institute's facilities. Mrs Shirley Richens provided skilled secretarial assistance.

REFERENCES

Ahlborg, G., Felig, P., Hagenfeldt, L., Hendler, R., and Wahren, J. (1974). Substrate turnover during prolonged exercise in man. *J. Clin. Invest.*, **53**, 1080.

Armitage, P. (1971). *Statistical Methods in Medical Research*, p. 217. Oxford and Edinburgh: Blackwell Scientific Publications.

Berman, M. C., Harrison, G. G., Bull, A. B., and Kench, J. E. (1970). Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. *Nature* (*Lond.*), **23**, 531.

Bradley, S. E. (1962). Hepatic blood flow; in *Handbook of Physiology, Circulation*, vol. 3, p. 1387. Washington, D.C.: American Physiological Society.

Cohen, R. D., and Iles, R. A. (1977). Lactic acidosis: some physiological and clinical considerations. *Clin. Sci. Molec. Med.*, **53**, 405.

—— Woods, H. F. (1976). *Clinical and Biochemical Aspects of Lactic Acidosis*, p. 88. Oxford and Edinburgh: Blackwell Scientific Publications.

Czok, C., and Lamprecht, R. V. W. (1970). In *Methods of Enzymatic Analysis* (ed. H. U. Bergmeyer), 2nd edn, p. 1407. Berlin: Springer-Verlag.

Denny, H. R., and Lucke, J. N. (1977). Anaesthetic and surgical technique for bilateral adrenalectomy in stress-sensitive pigs. *Res. Vet. Sci.*, **23**, 372.

Duncombe, W. G. (1964). The colorimetric microdetermination of non-esterifield fatty acids in plasma. *Clin. Chim. Acta*, **9**, 122.

Eggstein, M., and Kuhlmann, E. (1974). In *Methods of Enzymatic Analysis* (ed. H. U. Bergmeyer), 3rd edn, p. 1825. New York and London: Academic Press.

Garby, L., and Vuille, J. C. (1961). The amount of trapped plasma in a high-speed microcapillary haematocrit centrifuge. *Scand. J. Clin. Lab. Invest.*, **13**, 642.

Gronert, G. A., and Theye, R. A. (1976). Halothane-induced porcine malignant hyperthermia: metabolic and hemodynamic changes. *Anesthesiology*, **44**, 36.

—— —— Milde, J. H., and Tinker, J. H. (1978). Catecholamine stimulation of myocardial oxygen consumption in porcine malignant hyperthermia. *Anesthesiology*, **49**, 330.

Hems, R., Ross, B. D., Berry, M. N., and Krebs, H. A. (1966). Gluconeogenesis in the perfused rat liver. *Biochem. J.*, **101**, 284.

Hohorst, H. J. (1962). In *Methods of Enzymatic Analysis* (ed. H. U. Bergmeyer), 1st edn, p. 622. Berlin: Springer-Verlag.

Iles, R. A., Cohen, R. D., Rist, A. H., and Baron, P. G. (1977). The mechanism of inhibition by acidosis of gluconeogenesis from lactate in rat liver. *Biochem. J.*, **164**, 185.

Jones, E. W., Nelson, T. E., Anderson, I. L., Kerr, D. D., and Burnap, T. K. (1972). Malignant hyperthermia of swine. *Anesthesiology*, **36**, 42.

Kalant, N., Leibovici, T., Rohan, I., and McNeill, K. (1978). Effect of exercise on glucose and insulin utilisation in the forearm. *Metabolism*, **27**, 333.

Lloyd, M. H., Iles, R. A., Simpson, B. R., Strunin, J. M., and Cohen, R. D. (1973). The effect of simulated metabolic acidosis on intracellular pH and lactate metabolism in the isolated perfused liver. *Clin. Sci. Molec. Med.*, **45**, 543.

Lucke, J. N., Hall, G. M., and Lister, D. (1976). Porcine malignant hyperthermia. I: Metabolic and physiological changes. *Br. J. Anaesth.*, **48**, 297.

Owen, O. E., Morgan, A. P., Kemp, H. G., Sullivan, J. M., Herrera, M. G., and Cahill, G. F. (1967). Brain metabolism during fasting. *J. Clin. Invest.*, **46**, 1589.

Rowell, L. B. (1974). Measurement of indocyanine green; in *Dye Curves: The Theory and Practice of Indicator Dilution* (ed. D. A. Bloomfield), 1st edn, p. 209. Aylesbury, England: H. M.+M. Medical and Scientific Publishers.

Wahren, J., Felig, P., Ahlborg, G., and Jorfeldt, L. (1971). Glucose metabolism during exercise in man. *J. Clin. Invest.*, **50**, 2715.

—— —— Cerasi, E., and Luft, R. (1972). Splanchnic and peripheral glucose and amino acid metabolism in diabetes mellitus. *J. Clin. Invest.*, **51**, 1870.

Werner, W., Rey, H. G., and Wielinger, H. (1970). A micro-method for the determination of the blood glucose concentration. *Z. Analyt. Chem.*, **252**, 224.

Williamson, D. H. (1974). In *Methods of Enzymatic Analysis* (ed. H. U. Bergmeyer), 3rd edn, p. 1679. New York and London: Academic Press.

Wolfson, S. K. (1957). Isocitric and 6-phosphogluconic dehydrogenases in human blood serum. *Proc. Soc. Exp. Biol. Med.*, **96**, 231.

Zierler, K. L. (1961). Theory of the use of arterio-venous concentration differences for measuring metabolism in steady and non-steady states. *J. Clin. Invest.*, **40**, 2111.

HYPERTHERMIE MALIGNE DES PORCS. VII: METABOLISME HEPATIQUE

RESUME

On a fait des recherches sur le métabolisme hépatique de sept porcs Piétrains pendant une hyperthermie maligne (MH) porcine. Le débit sanguin hépatique estimé à diminué pendant la MH, mais une augmentation de l'extraction de l'oxygène a permis de maintenir la fixation de l'oxygène splanchnique. Il y a eu un important dégagement de glucose et de potassium émanant du foie pendant la MH ce qui a apporté une importante contribution à l'hyperglycémie et à l'hyperkaliémie. La mesure de la fixation hépatique des précurseurs de la gluconéogénèse, du lactate, du glycérol et de l'alanine, montre que le flux de glucose émanant du foie dérive essentiellement de la glycogénolyse. La fixation du lactate par le foie a augmenté pendant la MH et il n'y a eu aucune preuve de la production de lactate hépatique pendant l'acidose profunde comme avaient pu le laisser penser les études *in vitro* effectuées sur un foie isolé. Il n'y a eu aucune preuve d'anomalie majeure de la fonction hépatique pendant la MH des porcs.

MALIGNE HYPERTHERMIE BEI SCHWEINEN, VII: LEBERMETABOLISMUS

ZUSAMMENFASSUNG

Lebermetabolismus während maligner Hyperthermie (MH) bei Schweinen wurde bei sieben Pietrain-Schweinen untersucht. Der geschätzte Leberblutfluss sank während MH, aber ein Anstieg der Sauerstoffentnahme ermöglichte die Aufrechterhaltung der viszeralen Sauerstoffaufnahme. Während MH kam es zu einer starken Abgabe von Glukose und Kalium durch die Leber, wodurch ein wichtiger Beitrag zur Hyperglykämie und Hyperkalämie geleistet wurde. Die Messung der Leberaufnahme an Vorläufern von Glukoneogenese wie Laktat, Glyzerol und Alanin zeigte, dass die Glukoseausscheidung der Leber hauptsächlich vom Glykogenabbau herkam. Die Laktataufnahme durch die Leber stieg während MH an, und es gab keine Beweise für eine Leber-Laktatproduktion während der profunden Azidose, wie durch *in vitro*-Studien mit Leberpräparaten angedeutet worden war. Es gab keine Anhaltspunkte für grössere Leberfunktionsstörungen während MH bei Schweinen.

HIPERTERMIA MALIGNA EN PUERCOS. VII: METABOLISMO HEPATICO

SUMARIO

Se llevaron a cabo averiguaciones sobre el metabolismo hepático durante la hipertermia maligna (HM) porcina en siete puercos Pietrain. El flujo sanguíneo hepático estimado disminuyó durante la HM, pero un aumento de la extracción de oxígeno permitió la mantención de la captación de oxígeno espláncnico. Hubo una liberación amplia de glucosa y de potasio del hígado en la HM, lo que contribuyó considerablemente a la hiperglicemia y a la hiperpotasemia. Las mediciones de la captación hepática de los precursores de la gluconeogénesis, lactato, glicerol y alanina demostraron que la efusión de glucosa del hígado se debía mayormente a la glicogenólisis. La captación de lactato por el hígado aumentó durante la HM, y no hubo evidencia de una producción de lactato hepático durante la severa acidósis, así como lo hacían pensar los estudios *in vitro* en el hígado aislado. No hubo ninguna prueba de una anormalidad mayor de la función hepática durante la HM porcina.

Br. J. Anaesth. (1980), **52**, 19

24-HOUR ALTHESIN–FENTANYL ANAESTHESIA IN DOGS. TIME COURSE OF HAEMODYNAMIC CHANGES

G. MICHALOT, P. GIRARDET, F. GRIMBERT, D. PIASENTIN AND P. STIEGLITZ

SUMMARY

A 24-h anaesthetic using a constant flow infusion of Althesin, fentanyl and pancuronium was given to 10 artificially ventilated dogs. No statistically significant haemodynamic changes occurred during the study, suggesting that the technique may be of value in long-term physiological studies.

Most anaesthetic agents and techniques used during clinical or experimental studies result in unwanted effects which may influence the phenomena being studied (Rushmer, van Citters and Franklin, 1963; Vatner and Braunwald, 1975). A survey of the literature further reveals a paucity of reports of long-term anaesthesia (Muren, 1967; Poyart et al., 1970; Arfors, Arturson and Malmberg, 1971; Danielson et al., 1975; Sjostrom and Wulf, 1975). Since the introduction of Althesin and fentanyl in the practice of anaesthesia, many reports have assessed the favourable therapeutic ratio and the rapid recovery from these drugs when used separately. Their combination for clinical anaesthesia was studied during anaesthesia of several hours' duration with no increase in side-effects compared with the use of either agent alone (Du Caillar et al., 1975). The present study was to assess haemodynamic effects in dogs undergoing 24-h anaesthesia using this combination. An uncertain element was possible drug-induced histamine release with an anaphylactoid reaction (Child, Currie and Twissell, 1971; Lorenz et al., 1971; Davis and Pearce, 1972) from the use of Althesin in the dog.

MATERIALS AND METHODS

Ten mongrel dogs weighing 10–20 kg were anaesthetized with Althesin 5 ml i.v. without premedication; anaesthesia was maintained by continuous infusion of Althesin 0.2 ml kg^{-1} h^{-1}, fentanyl 8 μg kg^{-1} h^{-1} with pancuronium bromide 64 μg kg^{-1} h^{-1} in lactated Ringer and 10% glucose solution. The infusion rate was 4 ml kg^{-1} h^{-1}. The dogs were placed in the supine position, the trachea intubated and the lungs ventilated with room air 200 ml kg^{-1} min^{-1} using a volume pre-set ventilator (frequency 12 b.p.m.). Body temperature, monitored using a thermistor probe in the thoracic oesophagus, was kept stable by a thermoregulated heating blanket. A Thomson telco apparatus allowed monitoring of e.c.g. and systemic arterial pressure (right femoral artery). Pulmonary blood flow was measured by the thermodilution method using a Swan–Ganz flow-directed 7F thermodilution catheter (Edwards). This catheter also allowed measurement of the pulmonary arterial and wedge pressures, right atrial pressure, and sampling of blood from the right atrium and pulmonary artery. The right femoral artery was used for systemic arterial blood sampling. The placement of catheters was identified by x-ray and by analysis of the pressure traces.

Heparin 0.1 mg kg^{-1} h^{-1} i.v. was given to preserve catheter patency. Vascular pressures were measured with Statham P23 Db Transducers. An Edwards Lab. 9500 cardiac output computer was used for pulmonary blood flow measurement. The thermodilution curves were recorded on a Sefram apparatus for planimetry using the William's formula (Williams, O'Donavan and Wood, 1966). The pulmonary blood flow was taken as the mean of each set of several measurements performed at 1-min intervals without synchronizing the injection with the cardiac or respiratory cycle.

A Beckman oxygen analyser was used to determine oxygen fraction in the inspired gas. Blood-gas tensions were measured with a Radiometer ABL 1 apparatus; oxygen saturation and haemoglobin concentration with an IL CO-oxymeter and oxygen contents with a Lex-O_2-Con analyser. Total systemic vascular resistance (TSR) and pulmonary arteriolar

---

G. MICHALOT, M.D.; P. GIRARDET, M.D.; F. GRIMBERT, M.D.; D. PIASENTIN, M.D.; P. STIEGLITZ, M.D.; Département d'Anesthésie–Réanimation, Centre Hospitalier Universitaire de Grenoble, 38700—La Tronche, France.

0007–0912/80/010019–05 $01.00

© Macmillan Journals Ltd 1980

resistance (PAR) were calculated according to the following expressions:

$$\text{TSR (dyne s cm}^{-5}\text{ m}^{-2}) = \frac{\overline{\text{SAP}} - \text{RVEDP}}{\text{CO}} \times 80$$

$$\text{PAR (dyne s cm}^{-5}\text{ m}^{-2}) = \frac{\overline{\text{PAP}} - \text{PCWP}}{\text{CO}} \times 80$$

where CO = cardiac output; $\overline{\text{SAP}}$ = mean systemic arterial pressure; RVEDP = right ventricular end diastolic pressure; $\overline{\text{PAP}}$ = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure.

Oxygen consumption was calculated according to Fick's equation. Measurements were made after placement of the catheters and every 4 h for 24 h. Blood was sampled at the beginning and at the end of the experiment for measurement of serum electrolytes and enzymes. The depth of anaesthesia was assessed by detection of recovering reflexes (eyelid reflexes), tolerance of endotracheal tube and ventilation, and lack of reaction to surgical stimulation.

RESULTS

The data are summarized in table I. Two-way analysis of variance with a significance level of $P<0.05$ shows that only pulmonary capillary wedge pressure and pulmonary arterial pressure varied significantly over 24 h ($P<0.01$ and $P<0.025$ respectively). However, the slope of the regression lines corresponding to the overall points for each of these two pressures is not great ($\beta = 0.072$ and $\beta = 0.17$ respectively). Comparison of the slopes of individual regression lines (for each dog) showed no significant difference for pulmonary capillary wedge pressure, although there was a difference in pulmonary arterial pressure ($P<0.05$). Comparison between the individual correlation coefficients according to Fisher's method (Fisher, 1967) demonstrated

TABLE I. *Haemodynamic and respiratory measurements (mean ± SEM; n = 10) during 24-h anaesthesia with Althesin and fentanyl in dogs. CI = cardiac index; HR = heart rate; RVEDP = right ventricular end-diastolic pressure; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; SAP = systemic arterial pressure; TSR = total systemic resistance; PAR = pulmonary arterial resistance;* $P\bar{v}_{O_2} = P_{O_2}$ *measured in the pulmonary artery;* $\dot{V}_{O_2}$ *= oxygen consumption; pHa = arterial pH. * Two-way analysis of variance*

	Time (h)							Significance
	0	4	8	12	16	20	24	
CI	3.14	3.25	3.29	3.35	3.21	3.22	3.40	n.s.
(litre min^{-1} m^{-2})	0.31	0.18	0.24	0.18	0.24	0.26	0.24	
HR	175	166	171	165	190	176	185	n.s.
(beat min^{-1})	12	11	6	14	7	8	8	
RVEDP	1.21	2.36	2.29	2.79	3.64	3.57	2.29	n.s.
(mm Hg)	0.64	0.9	0.73	0.59	0.7	1.17	0.89	
PAP	15.5	20.43	18.93	20	19	20.43	22.14	$P<0.025$
(mm Hg)	0.98	0.95	1.87	2.06	1.84	2.01	2.11	
PCWP	3.50	5.14	5.36	5.14	5.00	5.64	6.00	$P<0.01$
(mm Hg)	0.79	0.4	0.36	0.63	0.72	0.59	0.49	
SAP	103.7	91.8	96.4	96.7	102.5	95.7	103.1	n.s.
(mm Hg)	3.56	5.31	1.4	2.88	4.59	2.97	4.64	
TSR	2747	2229	2355	2280	2519	2438	2474	n.s.
(dyne s cm^{-5} m^{-2})	283	202	166	136	155	341	260	
PAR	322	385	338	361	359	382	402	n.s.
(dyne s cm^{-5} m^{-2})	29	33	50	50	48	56	72	
Pa_{O_2}	9.79	9.80	10.29	10.49	10.29	10.24	9.32	n.s.
(kPa)	0.34	0.39	0.33	0.32	0.39	0.37	0.48	
$P\bar{v}_{O_2}$	6.05	6.23	6.31	6.24	5.91	6.19	5.89	n.s.
(kPa)	0.17	0.14	0.09	0.08	0.08	0.07	0.34	
$\dot{V}_{O_2}$	171.7	165.2	187.2	201	217.2	194.7	218.7	n.s.
(ml min^{-1} m^{-2})	23.5	8.04	16.6	10.8	17.7	15.8	9.2	
Pa_{CO_2}	5.08	4.88	4.69	4.71	4.45	5.11	5.12	n.s.
(kPa)	0.32	0.23	0.27	0.31	0.25	0.41	0.27	
pHa	7.32	7.34	7.36	7.36	7.39	7.34	7.34	n.s.
	0.02	0.02	0.02	0.01	0.02	0.03	0.02	

homogeneity, which means that the individual correlation coefficients r were from the same ρ. However ρ was not significantly different from zero at the 5% level. Therefore, we conclude that these two measurements were essentially stable.

DISCUSSION

The technique described in the present study was associated with remarkable haemodynamic stability. Several authors have already reported lack of cumulative side-effects of Althesin (Du Caillar et al., 1975), corroborating experimental studies of the kinetics and metabolism of the drug (Child, Currie and Twissell, 1971; Card, McCullogh and Pratt, 1972). Liu and colleagues (1976) clearly showed in the dog that large doses of fentanyl (0.05 to 0.15 mg kg^{-1}) given as a constant infusion were necessary to produce significant cardiovascular changes. However, in a clinical study, Du Caillar and colleagues (1978) demonstrated progressively increasing plasma concentrations of fentanyl 45 min after the continuous infusion of an Althesin–fentanyl mixture, throwing some light on current concepts of fentanyl metabolism (Van Wijngaarden and Soudijn, 1968; Michiels, Hendricks and Heykants, 1977; Schleimer et al., 1978). These findings were corroborated by Hug (1978), who reported increasing plasma concentration of fentanyl following repeated administration of a standard dose. Thus, it is of interest to know if side-effects occur in the course of a long anaesthetic using fentanyl. The choice of the dog as an animal model might appear inappropriate since cremophor EL, the solvent for Althesin, has been thought to be responsible for anaphylactoid reaction in dogs. Indeed anaphylactoid reactions were demonstrated in the dog following injection of polymeric compounds (Krantz et al., 1948), but the frequency of adverse reactions to Althesin in this species has not been established. In our study none of the dogs showed signs of hypersensitivity. The doses of Althesin and fentanyl were determined during preliminary investigations without pancuronium and we found that dogs could endure marked surgical stimulation without responding; pancuronium bromide was used to counter residual spontaneous ventilatory movements and thoracic rigidity. Changes in blood oxygen and carbon dioxide tensions may be important factors influencing the time course of haemodynamic variations (Carson et al., 1965). In the present study, the ventilatory pattern was set so that arterial P_{CO_2} and pH were approximately in the normal range for the dog (Mitruka and Rawnsley, 1977). The perfusion rate was calculated to equal the normal urinary output in dog (Arfors, Arturson and Malmberg, 1971; Mitruka and Rawnsley, 1977). Our results compared with normal values in the dog (Mitruka and Rawnsley, 1977) show a greater cardiac index and heart rate—known effects when using Althesin separately (Patschke et al., 1976). The systolic index did not vary, the cardiac output in the dog being regulated through variations in heart rate (Rushmer, van Citters, and Franklin, 1963). The systemic arterial pressures were within the normal range, whereas the pressures in the pulmonary circulation were greater than normal, as previously reported with Althesin alone (Patschke et al., 1974; Patschke et al., 1976). Therefore, the haemodynamic values under Althesin–fentanyl anaesthesia were similar to those observed with administration of a single injection of Althesin. In particular, we did not observe bradycardia or systemic arterial hypotension which has been reported following administration of fentanyl (Kriffa, Moret and Gemperle, 1971; Liu et al., 1976), probably in part because of dose dependence (Liu et al., 1976). Similar observations were made during later experiments performed under the same technique in our laboratory (Grimbert et al., 1978). The stability of the preparation over 24 h would be satisfactory for physiological studies of such duration.

REFERENCES

Arfors, K. E., Arturson, G., and Malmberg, P. (1971). Effect of prolonged chloralose anaesthesia on acid–base balance and cardiovascular functions in dogs. *Acta Physiol. Scand.*, **81**, 47.

Card, B., McCulloch, R. J., and Pratt, T. (1972). Tissue distribution of CT 1341 in the rat. An autoradiographic study. *Postgrad. Med. J.*, **48**, (Suppl. 2), 34.

Carson, S. A. A., Chorley, G. E., Hamilton, F. N., Lee, D. C., and Morris, L. E. (1965). Variation in cardiac output with acid-base changes in the anesthetised dog. *J. Appl. Physiol.*, **20**, 948.

Child, K. J., Currie, J. P., and Twissell, D. J. (1971). The pharmacological properties in animals of CT 1341, a new steroid anaesthetic agent. *Br. J. Anaesth.*, **43**, 2.

—— Gibson, W., Harny, G., and Hart, J. W. (1972). Metabolism and excretion of CT 1341 in the rat. *Postgrad. Med. J.*, **48**, (Suppl. 2), 37.

Danielson, B., Grangsjo, G., Karlmark, B., Ulfendahl, H. R., and Wolgast, M. (1975). Acid–base status in dogs during long term anaesthesia. *Uppsala J. Med.*, **80**, 77.

Davis, R., and Pearce, D. R. (1972). An introduction to Althesin (CT 1341). *Postgrad. Med. J.*, **48**, (Suppl. 2), 13.

Du Caillar, J., Deschodt, J., Bessou, D., and Cabanel, P. (1975). Anesthésie à débit constant par l'association Alfatésine–Fentanyl. *Ann. Anesthesiol. Franç.*, **16**, 331.

Du Cailar, J., Mathieu-Daube, J. C., Deschodt, J., Barlet, H., and Kienlen, J. (1978). Etude de la concentration plasmatique du Fentanyl pendant et après son administration à débit constant. *Ann. Anesthesiol. Franç.*, **19**, 761.

Fisher, R. A. (1967). In *Statistical Methods*, 6th edn (eds G. W. Snedecor and W. G. Cocheran), p. 185. Ames: Iowa State University Press.

Grimbert, F., Girardet, P., Michalot, G., Dyon, J. F., and Alibeu, J. P. (1978). Validation of a thermodilution technique for pulmonary blood flow rate measurement during partial veno-arterial bypass. *Bull. Eur. Physiopathol. Resp.*, **14**, 639.

Hug, C. C. (1978). Pharmacokinetics of drugs administrated intravenously. *Anesth. Analg. (Cleve.)*, **57**, 704.

Krantz, J. C., Carr, C. J., Bird, J. G., and Cook, S. (1948). Sugar alcohols. XXVI: Pharmacodynamic studies of polyoxyalkylene derivatives of hexitol anhydride partial fatty acid esters. *J. Pharmacol. Exp. Ther.*, **93**, 188.

Kriffa, T., Moret, P., and Gemperle, M. (1971). Les effets de l'anesthésie générale séquentielle sur le système cardiovasculaire du chien. *Ann. Anesthesiol. Franç.*, **12**, 1.

Liu, W. S., Bidway, A. V., Stanley, T. H., and Isern-Amaral, J. (1976). Cardiovascular dynamics of large doses of Fentanyl and Fentanyl plus N_2O in the dog. *Anesth. Analg. (Cleve.)*, **55**, 168.

Lorenz, W., Meyer, R., Doenicke, A., Schmal, A., Reimann, H. J., Hutzel, M., and Werle, E. (1971). Species specificity of histamin-release from mast cell stores by cremophor-EL. *Naunyn-Schmiedebergs Arch. Pharmakol.*, **269**, 417.

Michiels, L. J. M., Hendricks, R., and Heykants, J. (1977). A sensitive radioimmunoassay for fentanyl plasma levels in dogs and man. *Eur. J. Pharmacol.*, **12**, 153.

Mitruka, B. M., and Rawnsley, H. M. (1977a). *Clinical Biochemical and Hematological Reference Values in Normal Experimental Animals*, pp. 5, 6, 240. New York: Masson.

Muren, A. (1967). Prolonged continuous anaesthesia. *Acta Anaesthesiol. Scand.*, **11**, 231.

Patschke, D., Bruckner, J. B., Genthmann, V. W., Tarnow, J., and Weymar, A. (1974). Influence of Althesin on coronary blood flow and myocardial oxygen consumption in dogs. *Acta Anaesthesiol. Scand.*, **18**, 23.

—— Hess, W., Tarnow, J., and Weymar, A. (1976). Effect of fentanyl and Althesin on hemodynamic inotropism of heart and myocardial oxygen consumption in dogs. *Acta Anaesthesiol. Scand.*, **18**, 23.

Poyart, F., Gaudebout, C., Blayo, M. C., Vallois, J. M., and Pocidalo, J. J. (1970). Adequate cardio-respiratory functions in mechanically ventilated dogs. *Respir. Physiol.*, **9**, 318.

Rushmer, R. F., van Citters, R. L., and Franklin, D. L. (1963). Some axioms, popular notions and misconceptions regarding cardiovascular control. *Circulation*, **27**, 118.

Schleimer, R., Benjamini, E., Eisele, J., and Henderson, G. (1978). Pharmocokinetics of fentanyl as determined by radioimmunoassay. *Clin. Pharmacol. Ther.*, **23**, 188.

Sjostrom, B., and Wulf, K. E. (1975). Influence of long-term anesthesia on regional blood flow distribution and hemodynamics in the dog. *Eur. Surg. Res.*, **7**, 1.

Van Wijngaarden, I., and Soudijn, W. (1968). The metabolism and excretion of the analgesic fentanyl (R 4263) by Wistar rats. *Life Sci.*, **7**, 225.

Vatner, S. F., and Braunwald, E. (1975). Cardiovascular control mechanisms in the conscious state. *N. Engl. J. Med.*, **293**, 970.

Williams, J. C. P., O'Donavan, T. P. B., and Wood, E. H. (1966). A method for calculation of areas under indicator dilution curves. *J. Appl. Physiol.*, **21**, 695.

ANESTHESIE DE CHIENS A L'ALTHESINE-FENTANYL PORTANT SUR 24 H: PORTEE DES CHANGEMENTS HEMODYNAMIQUES

RESUME

Dix chiens, ventilés artificiellement, ont reçu pendant 24 h une anesthésie à base d'althésine, de fentanyl et de pancuronium par infusion à débit constant. Il n'y a eu aucun changement hémodynamique statistiquement significatif pendant l'etude, ce qui semble indiquer que cette technique peut présenter un intérêt pour les études physiologiques à long-terme.

VIERUNDZWANZIGSTÜNDIGE ALTHESIN-FENTANYLNARKOSE BEI HUNDEN: ZEITABLAUF HÄMODYNAMISCHER VERÄNDERUNGEN

ZUSAMMENFASSUNG

Eine 24stündige Narkose mit konstanter Infusion von Althesin, Fentanyl und Pancuronium wurde 10 kunstlich belufteten Hunden verabreicht. Im Verlauf dieser Studie kam es zu keinen statistisch wesentlichen Veränderungen hämodynamischer Art, was anzeigt, dass diese Methode für langfristige physiologische Studien von Nutzen sein könnte.

ANESTESIA DE 24 H POR ALTESINA-FENTANILO EN PERROS: EVOLUCION TEMPORAL DE CAMBIOS HEMODINAMICOS

SUMARIO

Se administró un anestético de 24 h a 10 perros artificialmente ventilados al usar una infusión de flujo constante de Altesina, fentanilo y pancuronio. No ocurrieron cambios hemodinámicos algunos que tuvieran significado desde el punto de vista estadístico durante el estudio, lo que hace pensar que dicha técnica puede tener valor en estudios fisiológicos a largo plazo.

Br. J. Anaesth. (1980), **52**, 23

EFFECT OF BILIARY EXCRETION ON KETAMINE ANAESTHESIA IN THE RAT

S. J. IRELAND AND A. LIVINGSTON

SUMMARY

Ligation of the common bile duct in rats resulted in a significant prolongation of ketamine sleeping time and a significant increase of plasma concentration of ketamine and its N-demethylated metabolite, when compared with sham-operated control animals. The treated animals also showed significant increases of plasma bilirubin and glutamate pyruvate transaminase. Cannulation of the common bile duct in rats allowed collection of samples of bile which showed high concentrations of ketamine and its N-demethylated metabolite very shortly after i.p. injection of ketamine, the amount of ketamine alone accounting for 10% of the injected dose after 2 h; including the metabolite up to 25% of the injected dose could be accounted for. In view of this we would suggest that ligation of the bile duct in rats produced a prolongation of ketamine anaesthesia by increasing plasma concentrations through interference with a major excretory route for the drug and its main metabolite.

Ketamine is metabolized by the liver (Chang, Dill and Glazko, 1965) and it has been shown that pentobarbitone pretreatment can shorten the duration of anaesthetic action (Piel, Aldrete and Jones, 1969), indicating a role for hepatic metabolism in the duration of action of this drug. Several studies have indicated that tolerance to ketamine may develop in a variety of species, such as man (Bjarnsen and Corssen, 1967; Cronin et al., 1972; Bennett and Bullimore, 1973), monkey (Bree, Feller and Corssen, 1967) and rats (Douglas and Dagirmanjian, 1975), and it has been shown that increased hepatic metabolism plays an important part in the development of tolerance to ketamine (Livingston and Waterman, 1976, 1977, 1978a). As an extension to the studies on hepatic metabolism, a preliminary study on the effects of bile duct ligation on the duration of ketamine anaesthesia (Livingston and Waterman, 1978b) indicated that anaesthesia was significantly prolonged when the ketamine was given only 2 h after the ligation. This observation led to the suggestion that biliary excretion of the drug may be a factor in the termination of its action, particularly since White and others (1976) have detected ketamine in the bile of rats following i.m. injection. This investigation was designed to examine the contribution of biliary excretion to the duration of anaesthetic action of ketamine.

METHODS

Albino Wistar rats (12-week-old females; body weight 190–260 g) from a cross-fostered inbred colony were fed water and a standard diet *ad libitum* and kept under constant temperature and light conditions.

Bile duct ligation experiments

Groups of rats were lightly anaesthetized with halothane (May and Baker Ltd) and the common bile duct was exposed and ligated (or not, in the case of the sham-operated animals) at the end nearer the duodenum. The incision was closed and the animals left for 1–2 h to recover from anaesthesia. The rats were then injected with ketamine (Ketalar, Parke Davis Ltd) 100 mg kg^{-1} i.p. and the sleeping time, that is the time between loss and return of the righting reflex, was measured. At the point of recovery the animals were killed by decapitation and a heparinized mixed blood sample was collected and the brain dissected out and weighed. Blood samples were centrifuged to obtain plasma which was frozen until assay, the brains were homogenized in 0.9% saline to give a 10% homogenate, centrifuged at 1500 *g* for 30 min and the frozen supernatant was stored until assay.

Ketamine and its N-demethylated metabolite were assayed in both plasma and brain samples by the gas–liquid chromatographic method described by Chang and Glazko (1972) using 2-amino-2-(*o*-bromophenyl)-2-methylamino cyclohexanone as internal standard.

S. J. IRELAND, B.SC.; A. LIVINGSTON, B.SC., B.VET.MED., PH.D., M.R.C.V.S.; Department of Pharmacology, Medical School, University of Bristol, University Walk, Bristol BS8 1TD.

0007-0912/80/010023-06 $01.00

© Macmillan Journals Ltd 1980

Plasma samples were assayed also for bilirubin (both direct and indirect) by a colorimetric method using a diazo reagent (Sigma kit 605) and serum transaminases (s.g.o.t. and s.g.p.t.) by a colorimetric method using phenylhydrazones of the oxaloacetic or pyruvic acids formed, respectively (Sigma kit 505).

In addition to the recovery experiments, groups of six rats were prepared in the same way and killed at 10, 20, 30, 50 and 70 min after the injection of ketamine and plasma concentrations of ketamine and its N-demethylated metabolite were measured in the test and sham-operated animals. Conjugated bilirubin and transaminases were also measured in the plasma from the animals killed 10 min after injection.

Bile collection experiments

Rats were lightly anaesthetized with 1% halothane using open circuit and the common bile duct was exposed and cannulated towards the liver with a fine polyethylene tube. The incision was closed and the cannula was secured to the skin with adhesive tape in a manner which facilitated bile flow along the cannula. The rats were placed on a heated pad and collection of spontaneously flowing bile for 10-min periods was commenced. Bile was collected during halothane anaesthesia for 30 min, the halothane was then withdrawn and a slow i.p. injection of ketamine 100 mg kg^{-1} was given over several minutes; this was necessary to prevent apnoea. Bile fractions were collected for a further 140 min. During the later stages (usually from the 60th min onwards) it was necessary to administer halothane to offset the recovery from ketamine. The bile samples were measured for volume and weight and kept frozen until extraction and assay for ketamine and the N-demethylated metabolites.

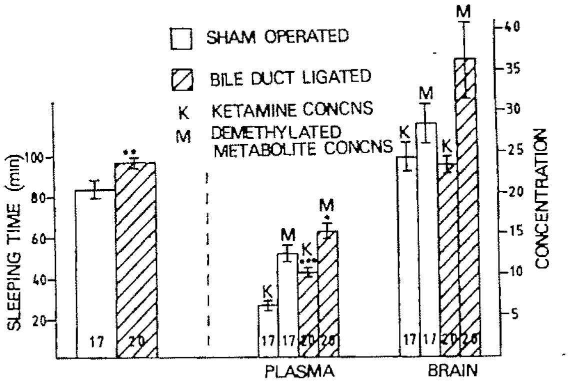


FIG. 1. Sleeping times and plasma (μg ml^{-1}) and brain (μg g^{-1}) concentrations of ketamine and the N-demethylated metabolite at recovery in bile duct-ligated and sham-operated rats injected with ketamine 100 mg kg^{-1} i.p. ($^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$). Mean ±SEM of number of animals indicated.

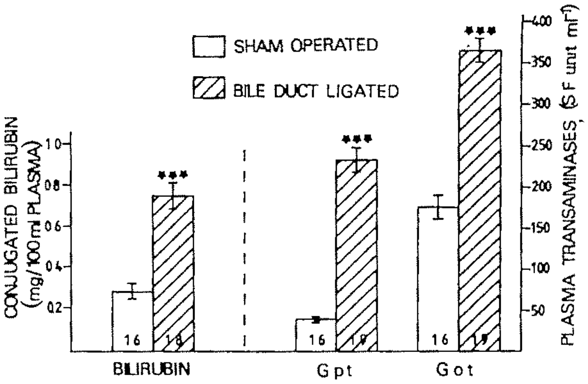


FIG. 2. Plasma concentrations of bilirubin, g.p.t. and g.o.t. at recovery in bile duct-ligated and sham-operated rats injected with ketamine 100 mg kg^{-1} i.p. ($^{***}P < 0.001$). Mean ± SEM of number of animals indicated.

RESULTS

In animals with ligated bile ducts, the experiments to measure sleeping time confirmed the earlier suggestion (Livingston and Waterman, 1978b) that, even after a period of 2 h or less, ligation significantly increased sleeping time after ketamine injection ($P < 0.01$) and it was found that, although brain concentrations at recovery were not significantly different between the two groups, the plasma concentration of ketamine ($P < 0.01$) and the demethylated metabolite ($P < 0.05$) were both significantly greater in the animals with ligated bile ducts at recovery (fig. 1). In the control animals sleeping times were not significantly different from unoperated animals receiving the same dose.

The estimates of bilirubin, s.g.o.t. and s.g.p.t. in the plasma at the time of recovery also showed significant differences between the ligated and sham-operated animals at the level $P < 0.001$ in all cases (fig. 2). The estimations of plasma ketamine and demethylated metabolite concentrations at various times after the injection of ketamine in sham-operated and bile duct-ligated animals also showed many significant differences between the two groups (fig. 3) with the increase in concentration of both agents becoming apparent after only 30 min in the bile duct-ligated animals. The measurement of plasma

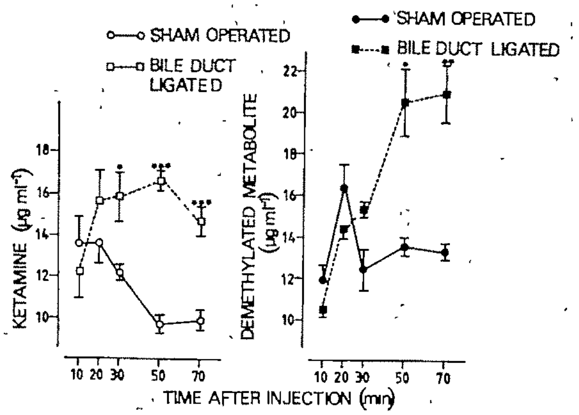


FIG. 3. Plasma concentrations of ketamine and the N-demethylated metabolite in bile duct-ligated and sham-operated animals at various times after injection of ketamine 100 mg kg⁻¹ i.p. (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). Mean ± SEM of three animals.

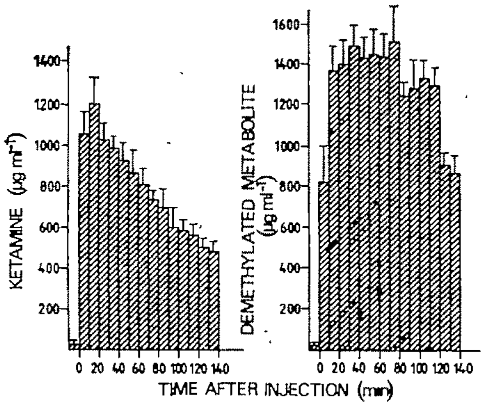


FIG. 4. Concentration of ketamine and the N-demethylated metabolite in bile of rats at various times after injection of ketamine 100 mg kg⁻¹ i.p. Mean ± SEM of five or six observations.

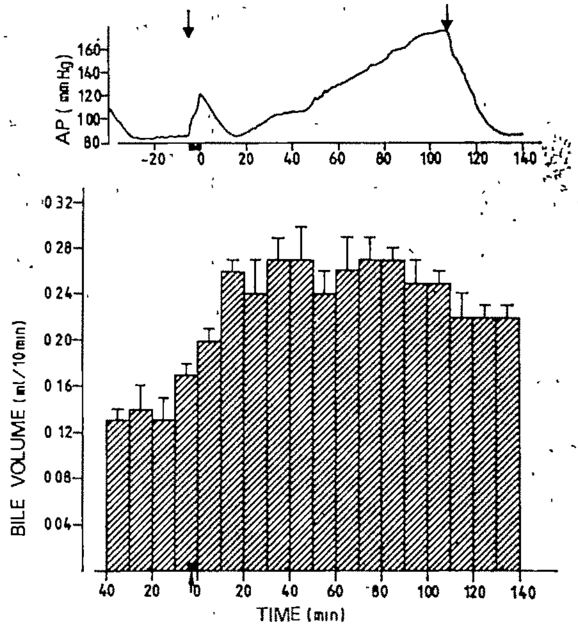


FIG. 5. Bile volume and typical arterial pressure recording at various times after the injection of ketamine 100 mg kg⁻¹ i.p. ■. Mean ± SEM of five or six observations.

conjugated bilirubin, g.o.t. and g.p.t. in the animals killed 10 min after the injection of ketamine showed a significant ($P < 0.05$) increase in bilirubin, in g.p.t. ($P < 0.01$) and an increase in g.o.t. which was not significant in the bile duct-ligated group compared with control.

The experiments using animals with cannulated bile ducts to collect bile showed the presence of both ketamine and its N-demethylated metabolite in high concentrations (fig. 4). Following the injection, the concentrations of ketamine increased rapidly, to reach a maximum during the 10–20-min collection period and thereafter declined in an exponential manner for the next 2 h. The concentrations of the demethylated metabolite increased to reach a maximum over the same time period, but then appeared to plateau for the next 2 h before declining, a pattern not dissimilar to that seen in the plasma. However, both agents were found in bile at concentrations about 100 times greater than that found in the plasma at the same time.

The volumes of bile produced were also shown to change during the period of the experiment (fig. 5) with a significant increase in volume of the first collection after the ketamine injection and this volume increase remained significantly increased throughout the period of the experiment. However, the density of the bile (mean 1.1 g ml⁻¹) did not change significantly during the experiment. These changes in bile volume may well reflect the changes which anaesthesia produced in the peripheral arterial pressure, since a parallel relationship between the two would seem to exist. The initial depression caused by halothane was rapidly reversed on its discontinuation, but the initial depression caused by the ketamine reduced it again, and it was followed by a slow but prolonged increase which persisted until halothane was reintroduced to maintain anaesthesia.

DISCUSSION

The significant increase in ketamine sleeping time following short-term ligation of the bile duct confirms the earlier work using male rats receiving a lower dose (Livingston and Waterman, 1978b). Although the brain concentrations of ketamine and the N-demethylated metabolite did not differ from those of animals at recovery, there was a significant increase in plasma concentrations of both agents at this time in the treated animals. Marietta and others (1976) have reported that, after the initial redistribution phase, the brain concentrations in control animals declined in parallel with the plasma concentrations, which might suggest that bile duct ligation can affect the distribution of the drug and its major metabolite in a significant manner.

The study of plasma concentrations of ketamine and the N-demethylated metabolite in treated and control animals indicated that the effect of ligation was to increase significantly the concentrations of both agents after a relatively short time. This observation led to the possibility that the effects were caused by a net reduction in the transfer of ketamine and its metabolite from the blood to the bile, although the possiblity of conjugation or active secretion could not be ignored. Net transfer could be reduced by an increase in the backflow of bile contents in the blood (Barber-Riley, 1963) and a decrease in bile production (Edlund, 1948). Bilirubin is conjugated in the liver and actively excreted into the bile (Smith, 1966). The observations that plasma bilirubin concentrations in the ligated animals were significantly increased both early in anaesthesia and at recovery would suggest that a similar circumstance involving active secretion might exist with regard to the transfer of ketamine and its metabolite.

Degenerative changes have been reported in the livers of rats within 24 h of experimental obstruction of the bile duct (Edlund, 1948), and ketamine has been reported to cause a reversible increase of serum g.o.t. and g.p.t. in dogs (McCarthy et al., 1965). However, in this study the concentrations in the ligated animals were always significantly greater than in the sham-operated controls, which indicated that the ligation, rather than the ketamine injection, was the cause of the increase of enzyme concentrations, although the period was short compared with that in the studies of Edlund (1948). Dogs have a gallbladder but rats do not, and it is possible that any pressure effects on the liver would be more obvious in rats. The studies on the time-course of changes in plasma concentrations and its metabolite would indicate that there was still considerable demethylation of ketamine proceeding, although the concentrations of g.o.t. and g.p.t. were increased.

The concentrations of ketamine and its demethylated metabolite present in the bile were large compared with plasma concentrations. During the 1st h, approximately 6.2% of an average 25-mg injected dose of ketamine was excreted unchanged in the bile, and about 10.3% during the first 2 h. If the amount of demethylated metabolite is included, the values increase to about 14.5% in the 1st h and 26.8% during a 2-h period which represents a considerable proportion of the injected dose. White and others (1976) reported that they could detect only 2.3% of the injected ketamine, in the unchanged form, in the bile during the first 1-h period. However, their rats were anaesthetized continuously with halothane and their work clearly demonstrates that halothane does affect the disposition and metabolism of ketamine, and so it is difficult to compare the figures from the two experiments; although the animals were only lightly anaesthetized before our experiments, it is possible that this could have some effect on the results. The figures for plasma and bile concentrations were obtained in two separate experiments and so care must be taken in interpretation, but it would appear that there is about a 100-fold greater concentration in bile than in plasma, which would put ketamine in the "group B" category of Brauer (1959), which contains water-soluble, polar substances with a molecular weight in excess of 300, and includes such compounds as bile salts, bilirubin–glucuronide and conjugates of many drugs and hormones (Smith, 1973). It is not clear, however, if the ketamine and its metabolite are excreted in a free or combined form.

The time-course of bile secretion of the demethylated metabolite was different from that of ketamine, but was close to that seen in the plasma of control animals, suggesting that although the plasma : bile concentration ratio for both drugs was about 1 : 100, the plasma concentration could influence the pattern of bile concentration.

The bile flow rate during halothane anaesthesia is very similar to the value of 0.124 ± 0.005 ml per 10 min reported by Vanlerenberghe and others (1968) for slightly larger male rats anaesthetized with pentobarbitone, and it is possible that the fluctuations in volume seen are influenced by anaesthetic-induced arterial pressure changes, although these effects are clearly not parallel. Both a reduction in hepatic blood flow and an increase in hepatic venous pressure can influence bile formation (Preisig et al., 1963), although the potential osmotic effects of ketamine and its metabolite on bile volume cannot be excluded. However, many other factors are known to affect bile flow, including, of course, the enterohepatic recirculation of bile salts which promote bile secretion (Sperber, 1959). Thus cannulation in these experiments should have caused a reduction in the observed flow.

The observations recorded here, that ligations of the bile duct caused a prolongation of anaesthesia and increased plasma concentrations of both ketamine and its N-demethylated metabolite, would suggest an excretory role for the bile in the metabolism of ketamine, particularly when the rapid appearance and high concentrations of ketamine and its N-demethylated metabolite are considered. These high concentrations would also suggest a process of active secretion of these agents into the bile; however, it is not possible at this stage to state whether ketamine and its metabolite are in a free or conjugated form.

REFERENCES

Barber-Riley, G. (1963). Measurement of capacity of biliary tree in rats. *Am. J. Physiol.*, **205**, 1122.

Bennett, J. A., and Bullimore, J. A. (1973). The use of ketamine hydrochloride anaesthesia for radiotherapy in young children. *Br. J. Anaesth.*, **45**, 197.

Bjarnsen, W., and Corssen, G. (1967). CI 581: a new non-barbiturate short-acting anesthetic for surgery in burns. *Mich. Med.*, **66**, 177.

Brauer, R. W. (1959). Mechanism of bile secretion. *J.A.M.A.*, **169**, 1462.

Bree, M. M., Feller, I. and Corssen, G. (1967). Safety and tolerance of repeated anesthesia with CI 581 (ketamine) in monkeys. *Anesth. Analg.* (*Cleve.*), **46**, 596.

Chang, T., Dill, W. A., and Glazko, A. J. (1965). Metabolic disposition of 2-(o-chlorophenyl)-2 methyl-amino cyclohexanone HCl (CI 581) in laboratory animals and in man. *Fed. Proc.*, **24**, 268.

—— Glazko, A. J. (1972). A gas chromatographic assay for ketamine in human plasma. *Anesthesiology*, **36**, 401.

Cronin, M. M., Bonsfield, I. D., Hewett, E. B., McLellan, I., and Boulton, T. B. (1972). Ketamine anaesthesia for radiotherapy in small children. *Anaesthesia*, **27**, 135.

Douglas, B. G., and Dagirmanjian, R. (1975). The effect of magnesium deficiency on ketamine sleeping times in the rat. *Br. J. Anaesth.*, **47**, 336.

Edlund, Y. (1948). In *Studies on the Carbohydrate Metabolism and Liver Protection Therapy in Experimental Biliary Obstruction. Acta Chir. Scand.*, **96** (Suppl. 136), 33.

Livingston, A., and Waterman, A. (1976). Effects of repeated doses of ketamine on sleeping times in rats. *Br. J. Pharmacol.*, **57**, 457P.

—— —— (1977). Self induction of metabolism by ketamine in the rat. *Br. J. Pharmacol.*, **60**, 296P.

Livingstone, A., and Waterman, A. (1978a). The development of tolerance to ketamine in rats and the significance of hepatic metabolism. *Br. J. Pharmacol.*, **64**, 63.

—— —— (1978b). Effects of bile duct ligation on ketamine anaesthesia in the rat. *Br. J. Pharmacol.*, **62**, 400P.

McCarthy, D. A., Chen, G., Kaump, D. M., and Ensor, C. (1965). General anesthetic and other pharmacological properties of 2-(o-chlorophenyl)-2-methylamino cyclohexanone HCl (CI 581). *J. New Drugs*, **5**, 21.

Marietta, M. P., White, P. F., Pudwill, C. R., Way, W. L., and Trevor, A. J. (1976). Biodisposition of ketamine in the rat. Self induction of metabolism. *J. Pharmacol. Exp. Ther.*, **196**, 536.

Piel, M. T., Aldrete, J. A., and Jones, G. (1969). Influence of enzyme induction on the sleeping times of rats. *Can. Anaesth. Soc. J.*, **16**, 538.

Preisig, R., Rankin, J. G., Sweeting, J., Williams, R., and Bradley, S. E. (1963). Bile formation during hepatic ischemia. *J. Clin. Invest.*, **42**, 966.

Smith, R. L. (1966). The bilary excretion and enterohepatic circulation of drugs and other organic compounds. *Prog. Drug Res.*, **9**, 299.

—— (1973). *The Excretory Function of Bile*, p. 94. London: Chapman and Hall.

Sperber, I. (1959). Secretion of organic anions in the formation of urine and bile. *Pharmacol. Rev.*, **11**, 109.

Vanlerenberghe, J., Trupin, N., Bel, C., Guislain, R., and Cassaigne, R. (1968). Action d'un modificateur de la perméabilitié capillaire sur la fonction biliaire du rat. *Therapie*, **22**, 1021.

White, P. F., Marietta, M. P., Pudwill, C. R., Way, W. L., and Trevor, A. J. (1976). Effects of halothane anesthesia on the biodisposition of ketamine in rats. *J. Pharmacol. Exp. Ther.*, **196**, 545.

EFFET DE L'EXCRETION BILIAIRE SUR L'ANESTHESIE A LA KETAMINE CHEZ LE RAT

RESUME

La ligature du canal biliaire chez les rats a eu pour résultat une prolongation significative du temps de sommeil provoqué par la kétamine, de même qu'une augmentation significative des concentrations de kétamine et de son métabolite N-déméthylé dans le plasma, par rapport aux animaux témoins ayant subi des opérations simulées. Les animaux traités ont aussi accusé des augmentations significatives de bilirubine et de pyruvate transaminase glutamique dans le plasma. La pose d'une canule sur le canal biliaire des rats a permis de ramasser des échantillons de bile montrant de fortes concentrations de kétamine et de son métabolite N-déméthylé immédiatement après l'injection i.p. de kétamine, la quantité de kétamine seule représentant au bout de 2 h, 10% de la dose injectée; y compris le métabolite jusqu'à 25% de la dose injectée. En raison de ce qui précède nous pouvons annoncer que la ligature du canal biliaire des rats produit une prolongation de l'anesthésie par la kétamine en augmentant ses concentrations dans le plasma, et en entravant de ce fait le chemin excrétif le plus important pour le médicament et son principal métabolite.

WIRKUNG VON GALLENAUSSCHEIDUNG AUF DIE KETAMINNARKOSE BEI RATTEN

ZUSAMMENFASSUNG

Eine Ligatur des Gallenganges bei Ratten führte zu einer wesentlichen Verlängerung der durch Ketamin bewirkten Schlafperiode und zu einem wesentlichen Anstieg der Ketamin-Plasmakonzentration und seines N-demethylisierten Metaboliten, verglichen mit Tieren mit simulierten Operationen an in einer Kontrollgruppe. Die behandelten Tiere zeigten auch wesentliche Anstiege von Plasmabilirubin und glutaminsaurer Pyruvat-Transaminase. Eine Kanülen-einfuhrung in den Gallengang von Ratten ermöglichte eine Sammlung von Gallenproben, die hohe Ketaminkonzentrationen und Konzentrationen des N-demethylisierten Metaboliten ganz kurz nach der Injektion von Ketamin zeigten, wobei allein die Ketaminmenge 10% der injezierten Dosis war—nach 2 Stunden einschliesslich des Metaboliten konnten bis zu 25% der injezierten Dosis nachgewiesen werden. Wir glauben daher, dass eine Ligatur des Gallenweges bei Ratten eine Verlängerung der Ketaminnarkose bewirkt, indem die Plasmakonzentrationen durch Interferenz mit einem Hauptausscheidungsweg für die Droge und deren Hauptmetaboliten erhoht werden.

EFECTO DE LA EXCRECION BILIAR EN LA ANESTESIA POR QUETAMINA DEL RATON

SUMARIO

La ligación del canal biliar común en ratones tuvo como resultado una prolongación significativa del tiempo de sueño con quetamina y un aumento significante de la concentración de quetamina en el plasma y de su metabolito N-desmetilado, cuando se la comparó con los animales de control de simulación. Los animales tratados demostraron también aumentos significativos de bilirubina y de transaminasa de piruvato glutámico en el plasma. La canulación del canal biliar común en ratones permitió recopilar muestras de bilis en la cual se encontraron altas concentraciones de quetamina y de su metabolito N-desmetilado, poco después de la inyección i.p. de quetamina, mientras la cantidad de quetamina sola representaba el 10% de la dosis inyectada después de 2 h; incluyendo al metabolito, se podía encontrar hasta el 25% de la dosis inyectada. En visto de lo que antecede, sugerimos que la ligación del canal biliar de los ratones produce una prolongación de la anestesia por quetamina, al incrementar las concentraciones en el plasma a través de la interferencia con una ruta excretoria mayor para la substancia y su principal metabolito.

Br. J. Anaesth. (1980), **52**, 29

MASS SPECTROMETER MEASUREMENT OF OXYGEN UPTAKE AND CARBON DIOXIDE EXCHANGE DURING CARDIOPULMONARY BYPASS

T. R. Abbott, B. Goodwin, G. Clark and G. J. Rees

SUMMARY

Oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) were measured continuously in four children during cardiopulmonary bypass, using the variation in concentration of a tracer gas, argon, as a measure of flow, and a mass spectrometer to monitor gas concentrations. Normal values for the ratio of $\dot{V}CO_2 : \dot{V}O_2$ ($= 0.8$) indicated that gas exchange equilibrium had been established following sudden changes in body temperature. During rapid cooling, 10% carbon dioxide is necessary to ensure carbon dioxide homeostasis within the body.

Oxygen uptake ($\dot{V}O_2$), and carbon dioxide output ($\dot{V}CO_2$) during cardiopulmonary bypass depend largely on the temperature of the body. When rapid cooling and warming of the body is achieved by means of a heat exchanger in the heart–lung machine, gas exchange will also be affected by the change of solubility of gases in liquids. Clinical reports emphasize the importance of maintaining adequate concentrations of carbon dioxide in the body during hypothermia in order to improve tissue perfusion by maintaining peripheral and cerebral vasodilatation, and to counteract the shift to the left of the oxygen dissociation curve (Burton, 1964; Brown and Sellick, 1965). These authors recommend the use of 5% carbon dioxide in oxygen in the oxygenator during cooling, but Johnston and others (1974) have suggested that at least 10% carbon dioxide is necessary at temperatures less than 30 °C to maintain normal carbon dioxide concentrations in the body. We have measured $\dot{V}O_2$ and $\dot{V}CO_2$ continuously in four patients, undergoing cardiopulmonary bypass and surgery for congenital heart disease, using 5% and 15% carbon dioxide in oxygen gas mixtures in the oxygenator. We wished to determine when gas exchange equilibrium occurred following sudden changes in temperature.

Mass spectrometry is being used increasingly in respiratory measurements, including non-invasive determination of cardiac output utilizing inert tracer gases (Zeidifard, Godfrey and Davies, 1976; Severinghaus, Ozanne and Lauderbough, 1978).

For the measurements described here, a mass spectrometer was used to monitor the difference in concentration of component gases in the gas streams flowing to and from the oxygenator. An insoluble tracer gas was included to allow the changes in gas flow from the oxygenator to be measured.

MATERIALS AND METHODS

The apparatus for cardiopulmonary bypass is shown schematically in figure 1A. During bypass, blood is circulated continuously by the action of the pump (P) through a standard cardiopulmonary bypass circuit. Venous blood passing to the oxygenator is tonometered to the tensions of the gas entering at (A), oxygenated blood passes through the bubble trap into the arterial pool and is recirculated, and excess gas passes out of the oxygenator at (B). The heat exchanger (H) allows temperature control and cooling of the blood.

Considering the parameters of gas exchange, the configuration of figure 1A can be represented by a simple-compartment model (fig. 1B). C represents the blood volume within the oxygenator and C_n the different compartments of the patient. The gas flow into the oxygenator at (A) is represented in the model by $\dot{V}I$, and the excess gas flow out of the oxygenator, which may include water and anaesthetic vapour components, is $\dot{V}E$.

If gas exchange in the lungs is taken to be negligible during bypass, then $\dot{V}O_2$ can be expressed as:

$$\dot{V}O_2 = \dot{V}I \, . \, FI_{O_2} - \dot{V}E \, . \, FE_{O_2} \qquad (1)$$

T. R. Abbott, M.B., CH.B., F.F.A.R.C.S.; B. Goodwin, PH.D.; G. Clark, M.B., CH.B., F.F.A.R.C.S.; G. Jackson Rees, M.B., CH.B., F.F.A.R.C.S.; Royal Liverpool Children's Hospital, Myrtle Street, Liverpool L7 7DG.
Correspondence to T. R. A.

0007-0912/80/010029-12 $01.00

© Macmillan Journals Ltd 1980

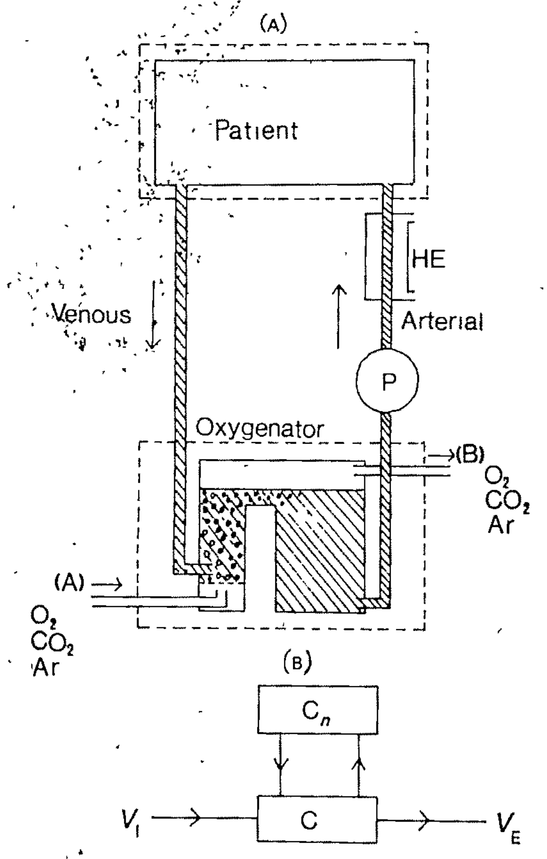


FIG. 1. A: The apparatus configuration for cardiopulmonary bypass; B: the apparatus configuration for cardiopulmonary bypass represented as a compartmental model.

A similar expression can be written for $\dot{V}_{CO_2}$.

The parameters $\dot{V}_I$, $F_{I_{O_2}}$ and F_{CO_2} of equation (1) can be measured easily, but the volume $\dot{V}_E$ may include water and anaesthetic vapours, so that direct measurement is less practical. The device adopted here to overcome this difficulty is to include an insoluble tracer component of known concentration (TR), in the inspired gas. Changes in concentration of tracer in the gas output reflect deviations of $\dot{V}_E$, from $\dot{V}_I$. Such deviation may result from uptake of a component of the input gas or from output of some additional component—water vapour or an anaesthetic agent for example. Stating this formally:

$$\dot{V}_E = \dot{V}_I \times \frac{F_{I_{TR}}}{F_{E_{TR}}} \qquad (2)$$

Here $F_{I_{TR}}$ and $F_{E_{TR}}$ are the fractional concentrations of the tracer in the input and output gas streams respectively.

Substituting for $\dot{V}_E$ in equation (1), the expression for oxygen uptake becomes:

$$\dot{V}_{O_2} = \dot{V}_I \left(F_{I_{O_2}} - \frac{F_{I_{TR}}}{F_{E_{TR}}}\right) . F_{E_{O_2}} \qquad (3)$$

Similarly, for carbon dioxide exchange,

$$\dot{V}_{CO_2} = \dot{V}_I \left(F_{I_{CO_2}} - \frac{F_{I_{TR}}}{F_{E_{TR}}}\right) . F_{E_{CO_2}} \qquad (4)$$

In the measurement of gas exchange reported here, the solution of equations (3) and (4) to obtain $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$, respectively is achieved by using the mass spectrometer to measure the concentration of expired oxygen, carbon dioxide and tracer gas components. The input concentration of each component is obtained from a previous analysis of the gas mixture. The input flowrate $\dot{V}_I$ is measured by passing the input gas through a conventional dry displacement gas meter; the method is detailed below.

The mass spectrometer used throughout the study was the Multi-Gas Monitor (MGM), Model MS2, marketed by The Medishield Corporation. The respiratory probe of the gas monitor was placed at the excess gas port B (fig. 1). The component gases were measured at the following mass peaks: oxygen at 32, the tracer gas argon (Ar) at 40 and carbon dioxide at 12 in order to avoid interference with nitrous oxide which has the same molecular weight, 44, as carbon dioxide. The resolution of the instrument was set so that peak overlap at adjacent peaks was less than 0.1%. Linearity of response has been reported previously as better than 1% (Goodwin, Holme and Leck, 1977; Goodwin, 1978). The instrument was calibrated against certified gas mixtures.

The data recording system is illustrated in figure 2. With a multiplexer accessory (peak follower) the mass spectrometer gave continuous analog outputs for the three gases measured which were recorded, with the patient's temperature, on chart recorders. For ease of computation the partial pressure measurements of carbon dioxide, oxygen and the tracer gas were recorded serially on a Facit paper tape punch for later analysis by computer. The serial record was obtained by means of an electro-mechanical switching unit (S) which continuously switches the digital voltmeter input to sample the three gas channels of the MGM and the patient's temperature (fig. 2); the sampling cycle was 30 s.

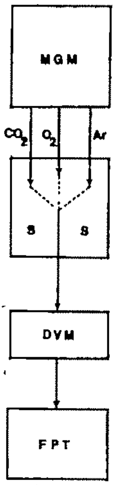


FIG. 2. Data recording system. MGM = Multi-gas monitor and multiplexer; S = switching unit; DVM = digital voltmeter; FPT = Facit punch tape recorder.

Choice of tracer gas

The ideal tracer gas for this form of investigation is one having a solubility which is low in comparison with the gases to be monitored. In this respect helium is outstanding, having a solubility approximately one-quarter of that for oxygen. A disadvantage of helium, however, is that because of the low ionization cross-section for this molecule, the mass spectrometer sensitivity is some 25% less in comparison with other gases.

In addition to this factor, consideration was given to the concept of using a tracer gas having solubility properties similar to oxygen, so that the measured oxygen exchange would reflect only the metabolic component of total oxygen exchange and would ignore uptake resulting from changes in solubility following changes in body temperature.

TABLE I. *Solubility of gas in water expressed as millilitre of gas dissolved per millilitre of water per* 760 *mm Hg gas pressure*

	10 °C	40 °C
Oxygen	0.037	0.022
Carbon dioxide	1.160	0.518
Argon	0.041	0.025

The solubility coefficients of oxygen, carbon dioxide and argon in water at 10 °C and 40 °C are given in table I. Accordingly, argon was selected as the tracer, since the solubility/temperature characteristic closely resembles that of oxygen. An additional advantage of argon is its high ionization cross-section. The gradient of the solubility/temperature characteristics for argon and oxygen are not precisely identical and therefore during rapid cooling there will be a small overestimate of metabolic oxygen exchange. With a temperature change from 39 to 20 °C this would be in the order of 1 ml per litre of blood/tissue.

In the case of carbon dioxide the solubility is about 40 times greater than that of argon; therefore, there will be a 2.5% error because of the solubility of argon on the estimation of that fraction of carbon dioxide uptake which results from enhanced solubility, when cooling from 40 to 10 °C.

Measurement of input gas flow rate

The rate of gas flow into the oxygenator was measured using a modified dry displacement gas meter in which the conventional dial register was replaced by a multiturn potentiometer. By connecting the potentiometer into a Wheatstone bridge circuit the total gas volume that has passed into the oxygenator is represented by an electrical analog signal which can be plotted on a chart recorder.

Many dry-gas meters show a degree of nonlinearity during each cycle of the internal mechanism. With the meter used here such non-linearity was shown by a symmetrical, cyclic deviation of the meter output, about the true linear curve. During the first half-cycle of the mechanism the reading is an overestimate of gas volume and, conversely, the volume is underestimated during the second half-cycle.

In order to avoid errors because of this nonlinearity, volume measurements were obtained at the completion of each cycle. For the meter used here, a complete cycle of the internal mechanism represented the passage of 57 litre of gas at atmospheric pressure and 23 °C. The average gas flow rate was then calculated by observing the time for completion of each cycle, indicated by incremental changes of 57 litre, from an initial "start of cycle".

The dry-gas meter was calibrated for gas flows in the range 2–5 litre min^{-1} using a water displacement method. Repeated measurements indicated a precision of ±2%, which is high for gas volume measurements, and is a result of our studies of the characteristics of the gas meter, and the limited dynamic range utilized.

The dry gas meter is positioned in the gas inlet line to the oxygenator, hence the volume measurement is made at a pressure above atmospheric. Since the mass spectrometer samples the expirate at or near atmospheric pressure, a correction was made to the dry-gas meter reading, based on the pressure of the gas input at A, figure 1.

Accuracy and calibration

The main sources of error in the method can be classified under three components:

(1) random error or instability of the mass reading;
(2) drift in the mass spectrometer sensitivity;
(3) error in the measurement of input gas flow.

Considering random error or instability and the mass spectrometer output for each of the gases oxygen, carbon dioxide and argon, the tracer gas was in the range 1.400–2.000 V throughout each experimental run. Taking the worst case of a random instability of ±20 mV on the reading for each gas (which corresponds to a minimum reading error of ±1%) and carrying this through the computation leads, in the case of oxygen, to a relative error of precision ranging from ±1 ml min^{-1} for uptakes less than 10 ml min^{-1} to ±2 ml min^{-1} for values exceeding 20 ml min^{-1}. Therefore, the absolute error in oxygen uptake measurements, which includes the tolerance on measurements of inspired flow rate $\dot{V}_I$, and the calibration gas certification, is estimated to be in the range 2–3 ml min^{-1}. A similar error can be estimated for carbon dioxide.

The error caused by random fluctuation in the mass spectrometer reading defines the minimum detectable gas exchange and the maximum accuracy that can be anticipated from the method. Drift in the mass spectrometer sensitivity may be anticipated to degrade the accuracy further and because of this the mass spectrometer calibration was checked after each experimental run. For monitoring periods up to 2 h the drift in sensitivity was not found to be significant. During longer monitoring periods the mass spectrometer was re-calibrated from time to time as conditions permitted. Calibration was performed using a certified gas mixture comprising oxygen, carbon dioxide and argon, the tracer gas.

RESULTS

In vitro

In order to evaluate the method under conditions as close as possible to the clinical setting, the oxygenator and external tubings of figure 1A were filled with distilled water (2.6 litre), and the venous-arterial conduits connected to form a continuous loop. A gas stream comprising 80% oxygen, 15% carbon dioxide and 5% argon was connected to the oxygenator at (A) (fig. 1A) and the temperature was measured at the venous input B using a thermistor probe. Using the heat exchanger, the water was cooled rapidly from 40° C to 10 °C and the resulting uptake of carbon dioxide and oxygen, resulting from increased solubility, was measured in the manner described. It was shown that, during rapid temperature changes of the order of 1 °C per minute, temperature gradients of up to 3 °C occur in the large body of liquid within the oxygenator, and this would preclude a direct comparison of measured gas exchange with that obtained from a trivial calculation from known solubilities data. However, the effect of temperature gradients can be reduced, and an indication of the precision of the method obtained, by taking the water temperature through a cycle, hence returning to the initial temperature conditions within the oxygenator. Accordingly, the water was reheated to 40 °C and the concomitant gas exchanged measured again.

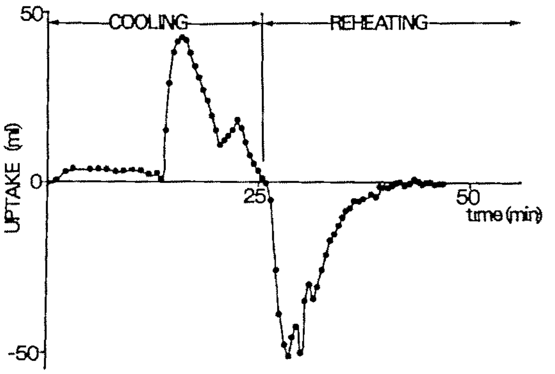


FIG. 3. Exchange in ml min^{-1} observed for carbon dioxide as a function of time, during successive cooling and heating of water.

The curve of figure 3 shows the exchange (ml min^{-1}) observed for carbon dioxide, as a function of time, during successive cooling and heating of the water. The area under the sections of the curve corresponding to cooling and heating of the water represents the total volume of carbon dioxide absorbed and desorbed respectively.

The difference in area between the two regions is potentially an indication of the dynamic precision of the method. Both areas were evaluated using

Simpson's Rule and a gas exchange of 292 and 300 ml was obtained for absorption and desorption phases respectively. The area difference of 8 ml corresponds to an error of 0.2 ml min^{-1} over the experimental period. There will, however, be an error in the absolute measurement of uptake of carbon dioxide as a result of the solubility of argon, as described above, and also an error from the temperature disequilibrium between different parts of the oxygenator prime. During rapid temperature changes, gradients of up to 3 °C were measured in different sites within the oxygenator. In considering this result, however, it should be noted that the gradient of the solubility curve at 40 °C and the accuracy of temperature measurement would preclude, on practical grounds, an area difference less than 2.4 ml, identical temperature gradients being assumed for the two equilibrium conditions at 40 °C.

CLINICAL APPLICATION AND MEASUREMENTS

Patients

Details of the four patients investigated are given in table II. Patient 1 was perfused at a constant temperature of 30 °C using 15% carbon dioxide. Patients 2 and 3 were cooled to approximately 21 °C with 15% and 5% carbon dioxide respectively, and patient 4 was cooled to 23 °C with 5% carbon dioxide and, following a period of circulatory arrest of 60 min, during reperfusion and rewarming, $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ were measured.

Procedure

The patients were premedicated with trimeprazine tartrate 1.0 mg kg^{-1} orally, 2 h before operation, followed by morphine 0.2 mg kg^{-1} and atropine sulphate 0.01 mg kg^{-1} given i.m. 1 h later. Anaesthesia was induced with thiopentone 4 mg kg^{-1} followed by tubocurarine 0.7 mg kg^{-1}, i.v. Orotracheal intubation was performed and anaesthesia was maintained using 30% oxygen and 70% nitrous oxide with IPPV. Cardiopulmonary bypass was established using roller pumps and a disposable bubble oxygenator, which was primed with fresh citrated blood, Hartmans solution 15–20 ml kg^{-1} and sodium bicarbonate to adjust the base excess to zero. Both caval veins were cannulated and snared. The lungs were not ventilated during perfusion, but distended at 5 cm H_2O CPAP with 100% oxygen. Blood flow rates were based on 2.4 litre/m^2 body surface area or 100 ml kg^{-1} and maintained constant throughout perfusion. Cooling and rewarming were carried out with the aid of a heat exchanger in the extracorporeal circuit, at a rate of 1 °C min^{-1}, and the temperature of venous blood at the oxygenator was measured using a Yellow Springs Model 421 probe (Lunding and Rygg, 1968). The blood in the oxygenator was circulated through a closed loop, in order to obtain base-line readings of gas flow and composition before perfusion of the patient. In patient 4, base-line readings were obtained during the period of circulatory arrest and measurements made only during re-warming.

RESULTS

Patient 1 (*fig.* 4): 15% *carbon dioxide in oxygen*

$\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ are expressed in millilitre per minute uptake. During recirculation before perfusion, there was an output of oxygen of approximately 8 ml min^{-1} and an uptake of carbon dioxide of 10 ml min^{-1}. The temperature of the blood in the oxygenator decreased from 35 °C to 26 °C during this time, but was maintained stable at 35 °C during cardiopulmonary bypass to exclude the effect of temperature change on $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$. As bypass commenced, there was a sudden large uptake of carbon dioxide which declined in an exponential manner to a stable output of 40 ml min^{-1}, after approximately 30 min. Oxygen uptake increased and stabilized after 15 min to 43 ml min^{-1}, or 4.3 ml kg^{-1} min^{-1} at 35 °C, which is comparable with

TABLE II. *Details of patients investigated*

Patient	Diagnosis	Age (yr/months)	Weight (kg)	Oxygenator gas			Gas flow (ml min^{-1})	Oxygenator	Prime volume (ml)
				O_2(%)	CO_2(%)	Ar(%)			
1 K. B.	Atrial septal defect	3 yr/8	10.0	80.0	15.0	5.0	2440	Rygg	1200
2 S. W.	Tetralogy of Fallot	1 yr/1	8.0	80.8	14.7	4.5	2457	Temptrol	800
3 M. P.	Aortic stenosis	8 yr/2	28.0	90.5	4.8	4.8	2355	Rygg	1500
4 N. B.	Transposition of great vessels	1 yr	9.9	90.6	4.8	4.7	3045	Temptrol	800

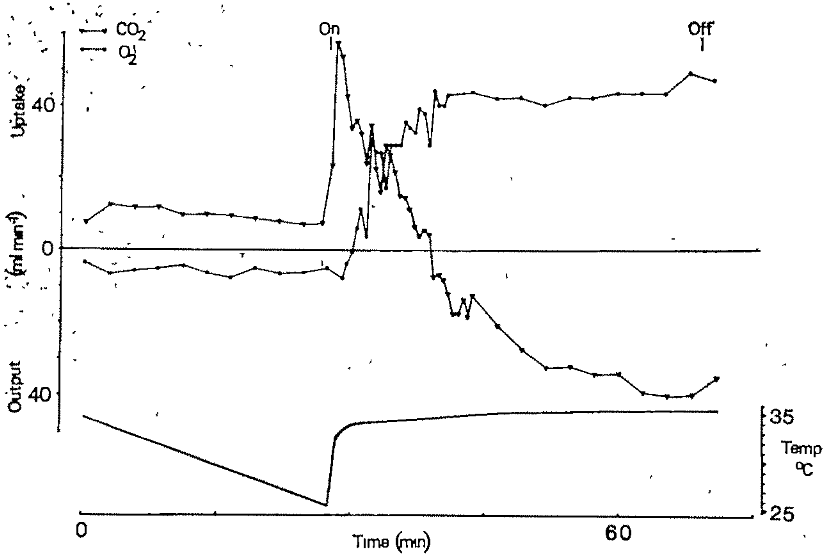


FIG. 4. Patient 1. Variation in oxygen and carbon dioxide exchange during cardiopulmonary bypass. Gas mixtures: oxygen 80%, carbon dioxide 15%, argon 5%

a value of 3.7 ml kg^{-1} min^{-1} derived from previous data (Abbott, 1977). The ratio of $\dot{V}CO_2$ to $\dot{V}O_2$ (RQ) during the last 15 min of perfusion was 0.79. Before perfusion, Pa_{CO_2} of the patient was 4.6 kPa, and after 30 min of perfusion with 15% carbon dioxide it was 13.3 kPa.

It is of interest to consider the raw data obtained from the mass spectrometer output for the three gases in this case.

The curves A, B and C of figure 5 show the mass spectrometer output for oxygen, carbon dioxide and argon, respectively. Because the curves represent the concentration of each gas in the output gas stream, they are approximately in anti-phase to the derived uptake curves of figure 4. This is particularly evident in the curve for carbon dioxide, the uptake curve of which (fig. 5B) is almost a reflection of the concentration curve in the time axis of figure 4.

The concentration curves are interdependent, since loss of a particular component will enhance the concentration of other components. At the commencement of perfusion there was a large uptake of carbon dioxide and oxygen, which is indicated in the curve of figure 5A, B by the rapid decrease in concentrations.

The marked uptake of these two gases would be expected to cause an increase in the concentration of the tracer gas. However, curve C (fig. 5) shows a marked reduction in argon concentration. A small reduction would be expected because of the solution of argon in the patient's blood and body tissue, but this could not possibly counteract the effect of uptake of carbon dioxide and oxygen.

The most probable cause of the reduced-argon concentration is the presence of an additional gas or water vapour in the output gas stream. The volume of gas involved is considerable, since it exceeds the uptake of carbon dioxide and the metabolic consumption of oxygen. In the absence of a fourth component in the output gas, the fractional concentration of oxygen, carbon dioxide and argon should sum to unity, since they are the only gases present. The volume fraction of the output gas flow contributed by the unknown gas or gases can therefore be easily obtained.

The calculated output gas flow is shown as a function of time in figure 6. The exponential decrease in the flow of additional gas and the relatively large volume of gas involved (600 ml) suggests that the "fourth gas" is mainly nitrous oxide (there could also be a nitrogen component) and figure 6 reflects a washout process through the oxygenator.

The data for this case were analysed retrospectively, hence no attempts were made to identify the gas using the mass spectrometer. Measurements made subsequently, however, confirm the presence of a large nitrous oxide component in the output gas following the onset of perfusion.

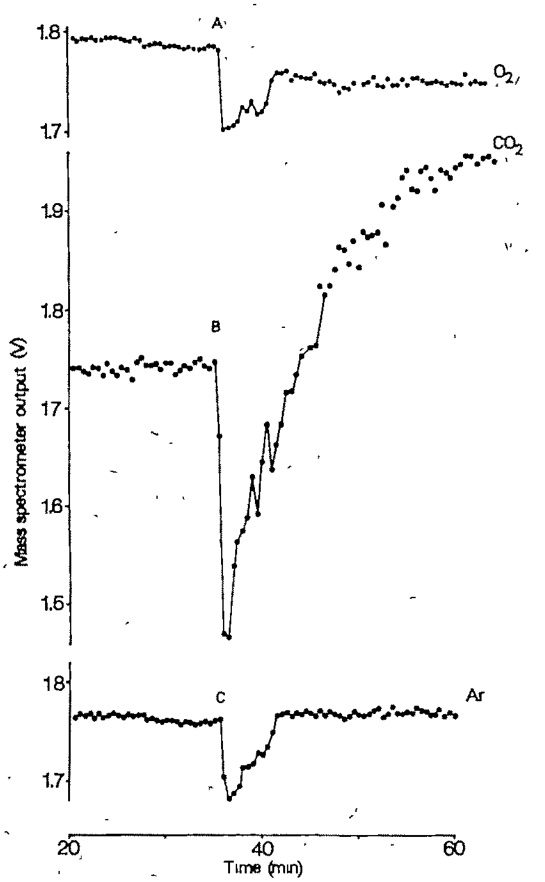


FIG. 5. Mass spectrometer outputs during cardiopulmonary bypass in patient 1. A = oxygen; B = carbon dioxide; C = argon.

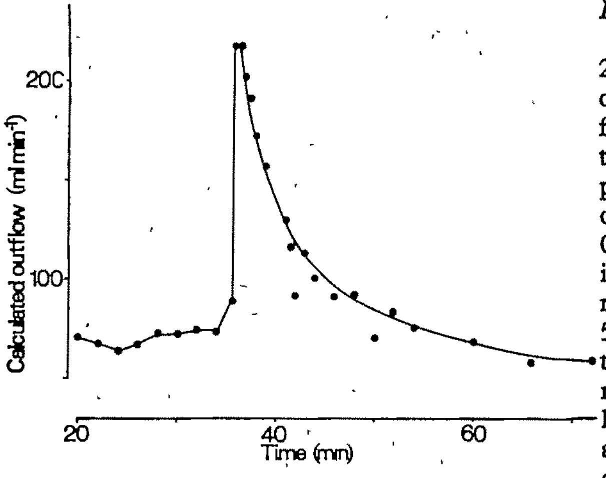


FIG. 6. The calculated output gas flow of unidentified gas (probably nitrous oxide) at the commencement of cardiopulmonary bypass in patient 1.

Patient 2 (*fig*. 7): 15% *carbon dioxide*

Before perfusion the oxygenator temperature decreased from 34 °C to 24 °C, and there was an uptake of oxygen of 6 ml min^{-1} which decreased to an output of 2 ml min^{-1}, and an uptake of carbon dioxide of 2–8 ml min^{-1}. The temperature increased rapidly at the commencement of bypass, was maintained at 35 °C to 35 °C for 5 min, then decreased rapidly to 22 °C over 15 min and remained stable at this temperature for 30 min, A–B, before rewarming commenced. As bypass started, oxygen uptake increased rapidly to 16 ml min^{-1} and then stabilized at 11 ml min^{-1}. Towards the end of this period, oxygen uptake gradually increased to 12.6 ml min^{-1}. There was no apparent uptake or output of carbon dioxide during the first 5 min of bypass at 34 °C, but rapid cooling was associated with a large uptake of carbon dioxide which reached 22 ml min^{-1} before gradually decreasing to 3 ml min^{-1} uptake before rewarming. On rewarming, carbon dioxide uptake rapidly changed to an output, associated with an increasing uptake of oxygen with the increase in temperature. At the termination of bypass, oxygen uptake was 29.6 ml min^{-1} or 3.6 ml kg^{-1} min^{-1} at 32 °C (calculated 3.0 ml kg^{-1} min^{-1}) and carbon dioxide output 16.8 ml min^{-1}. The ratio $\dot{V}\mathrm{CO_2} : \dot{V}\mathrm{O_2}$ at this point was 0.6, thus, although $\dot{V}\mathrm{O_2}$ had increased normally with temperature, $\dot{V}\mathrm{CO_2}$ was still less than was needed to produce a normal RQ. Certainly the ratio of $\dot{V}\mathrm{CO_2} : \dot{V}\mathrm{O_2}$ during this period of stable temperature at 22 °C was not normal, since there was a continuing uptake of carbon dioxide.

Patient 3 (*fig*. 8): 5% *carbon dioxide*

Before perfusion, the oxygenator temperature was 21.5 °C; it increased rapidly to 33 °C at the start of bypass then decreased to 21.5 °C over 15 min, followed by a period of stability (A–B, fig. 8) at this temperature for 45 min before rewarming. Before perfusion of the patient, there was an oxygen output of 7–10 ml min^{-1} and carbon dioxide output of 0.5–2.0 ml min^{-1}. As bypass started, oxygen uptake increased sharply to 68 ml min^{-1} before decreasing rapidly to an apparent output of 11 ml min^{-1} for 5 min as rapid cooling commenced. During this time the patient was still on partial bypass and some oxygen may have been exchanging via the lungs. Also, a large volume of cold blood was added to the oxygenator and would have been rapidly warmed, giving off oxygen. As total bypass was established, oxygen uptake stabilized at 22–25 ml min^{-1}, before decreasing to 14 ml min^{-1} as the temperature decreased and

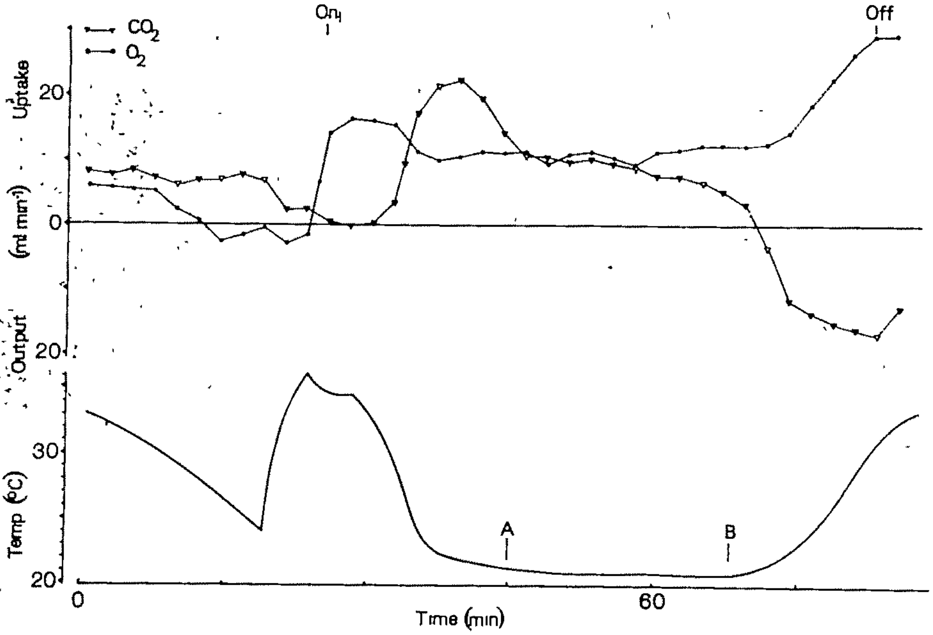


FIG. 7. Patient 2. Exchange of oxygen and carbon dioxide during cardiopulmonary bypass with rapid cooling to 22 °C. Gas mixture: oxygen 80.8%, carbon dioxide 14.7%, argon 4.5%. A–B: Temperature stable at 22 °C. "On" and "Off" indicate cardiopulmonary bypass.

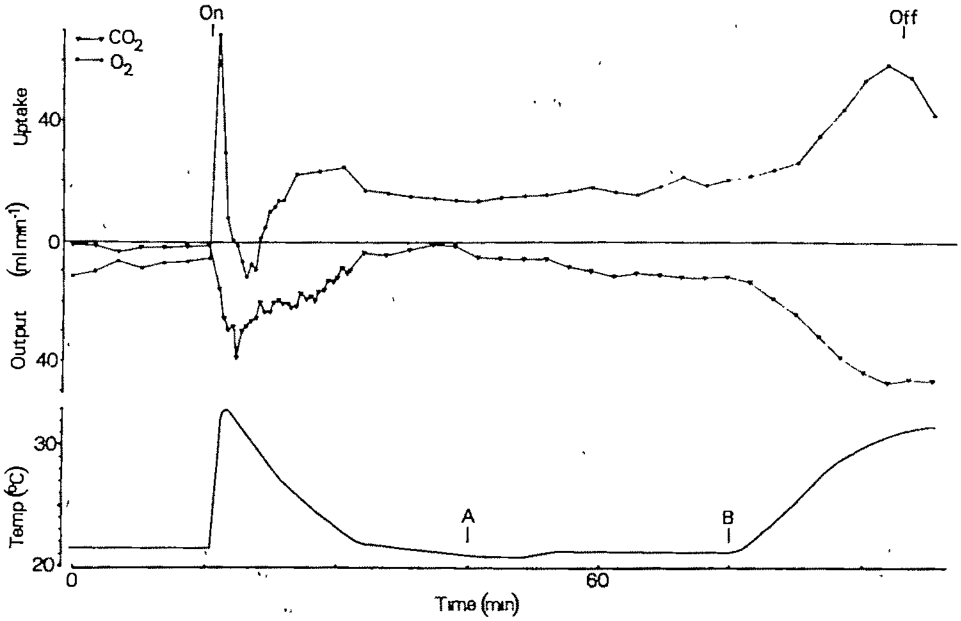


FIG. 8. Patient 3. Exchange of oxygen and carbon dioxide during cardiopulmonary bypass with rapid cooling to 22 °C. Gas mixture: oxygen 90.5%, carbon dioxide 4.8%, argon 4.8%. A–B: Temperature stable at 21.5 °C. "On" and "Off" indicate cardiopulmonary bypass.

stabilized. Towards the end of the period of hypothermia, oxygen uptake gradually increased to a maximum of 21 ml min^{-1} before rewarming. At the start of bypass, carbon dioxide output increased to 38 ml min^{-1} before decreasing to almost no output as the temperature decreased rapidly and stabilized. Then carbon dioxide output gradually increased until, at the end of the period of stable hypothermia at 21.5 °C, it reached 11.6 ml min^{-1}. The ratio $\dot{V}CO_2 : \dot{V}O_2$ at this point was 0.56. On rewarming, $\dot{V}O_2$ and $\dot{V}CO_2$ increased simultaneously, reaching peak values of 56 ml min^{-1} (2 ml kg^{-1} min^{-1}) and 45 ml min^{-1} (1.6 ml kg^{-1} min^{-1}) at 31 °C, an RQ of 0.8. The calculated $\dot{V}O_2$ at 31 °C was 2 ml kg^{-1} min^{-1}.

Patient 4 (*fig.* 9): 5% *carbon dioxide*

During the period of circulatory arrest, the oxygenator temperature was stable at 23 °C and there was an oxygen output of 2 ml min^{-1} with the carbon dioxide varying between an uptake and an output of 1–2 ml min^{-1}, both values within the limits of experimental error. When re-perfusion of the patient was commenced, the temperature was held constant between 23 °C and 24 °C for 12 min, during which time oxygen uptake initially increased to 32 ml min^{-1} before decreasing to 11 ml min^{-1} and carbon dioxide output increased to 35 ml min^{-1} before decreasing to 20 ml min^{-1}. The output of carbon dioxide was greater than the uptake of oxygen during this period, giving a ratio of $\dot{V}CO_2 : \dot{V}O_2$ varying between 1.8 and 2.3. During rewarming, $\dot{V}O_2$ increased to a maximum of 30 ml min^{-1} at 36 °C, whilst $\dot{V}CO_2$ reached a maximum of 26 ml min^{-1} at 36 °C, a ratio $\dot{V}CO_2 : \dot{V}O_2$ 0.86.

DISCUSSION

Previous studies have indicated an apparent wide variation in the relationship between body temperature and oxygen uptake when this is determined during cardiopulmonary bypass (Clowes et al., 1958; Starr, 1959; Bjork and Holmdahl, 1961; Lunding and Rygg, 1968; Abbot, 1977). These variations may be a result of the technical difficulties of measuring $\dot{V}O_2$, such as obtaining frequent blood samples for calculation of arterio–venous oxygen content difference, or in interpreting spirometric changes when respiratory gases are used. The incorporation of highly efficient heat exchangers in the extracorporeal circulation means that the body can be rapidly cooled and rewarmed via the blood stream. This inevitably causes large temperature gradients throughout the body (Brooks, 1964) and it is difficult

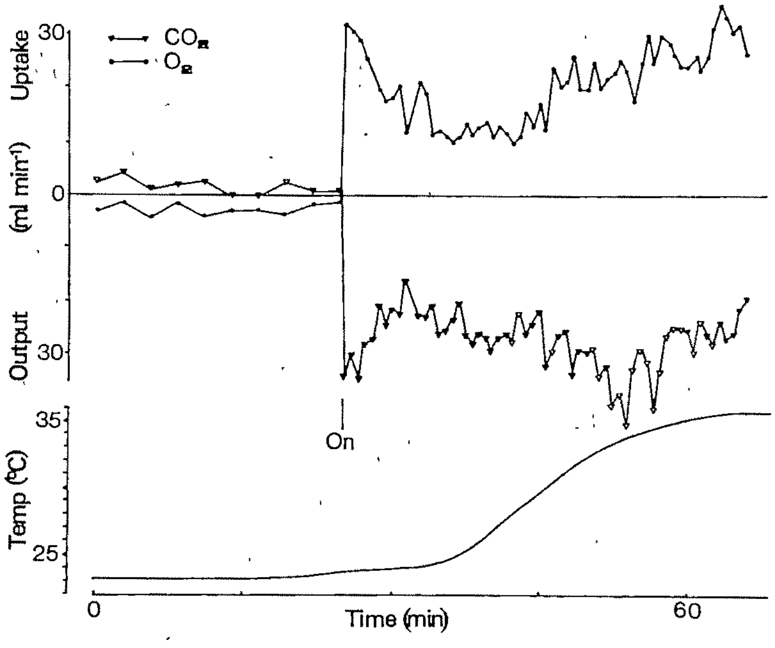


FIG. 9. Patient 4. Exchange of oxygen and carbon dioxide during cardiopulmonary bypass, whilst rewarming following a period of circulatory arrest of 60 min at 23 °C. Gas mixture: oxygen 90.6%, carbon dioxide 4.8%, argon 4.7%.

to decide which reference temperature to use. Also, sudden changes in blood temperature can be expected to result in rapid uptake or output of respiratory gases as a result of the effect of temperature on the solubility of gases in liquids. In this respect, carbon dioxide is likely to show more rapid changes, since its solubility coefficient is 30 times greater than that of oxygen. When hypothermia is induced by surface cooling, the process is slowed and the temperature gradients within the body will be smaller. Therefore, the relation to $\dot{V}O_2$ measured to body temperature may be closer and show less variation. Furthermore, Harris (1973) found that, following cardiopulmonary bypass using core cooling, $\dot{V}O_2$ was twice that obtained when cooling was largely or entirely by surface means. During the present investigation, the temperature of the venous blood was used as a reference point as it represented the average temperature of the blood which had perfused all the tissues. However, it was probably more representative of tissues and organs receiving a high blood flow than of low blood flow areas. If, following the induction of hypothermia by core cooling and maintenance of perfusion at a steady reference temperature, $\dot{V}O_2$ were to increase gradually, this could indicate that vascular beds of tissue which were poorly perfused initially, and therefore warmer than other areas, were slowly opening up. The use of carbon dioxide during cooling in concentrations even greater than 10% has been recommended in order to maintain tissue perfusion (Johnston et al., 1974).

In this study, before perfusion of the patient, base-line readings of gas flow and composition were obtained by circulating the priming fluid through the oxygenator and a closed loop. In each case, measurements indicated an uptake of carbon dioxide and an output of oxygen. Gas exchange during this period could be a result of:

(a) Gradual equilibration of the gas with blood in the oxygenator.

(b) The effect of a changing temperature on the solubility of gases in liquids and of large temperature differentials in the oxygenator circuit. This effect would be 30 times greater for carbon dioxide than for oxygen.

(c) The effect on the oxyhaemoglobin dissociation curve of varying temperature, carbon dioxide tension and pH.

The uptake of carbon dioxide may be explained in terms of the above factors and its high solubility coefficient. The output of oxygen of 2–8 ml min^{-1} is more difficult to account for completely. In patients 1 and 2 the temperature decreased by 10 °C during recirculation and this would shift the oxyhaemoglobin dissociation curve to the left, resulting in an uptake of oxygen at constant $P\text{O}_2$. However, the fluid in the oxygenator was equilibrated with 15% carbon dioxide in oxygen and $P\text{CO}_2$ 16.6 kPa was measured using standard blood-gas analysis. Callaghan and others (1961) have shown that an increasing carbon dioxide tension opposes the effect of hypothermia on the oxyhaemoglobin dissociation curve. A change in $P\text{CO}_2$ from 8 to 16 kPa would result in a decrease in haemoglobin saturation of approximately 10% at $P\text{O}_2$ 13.3 kPa, despite a decrease in temperature from 34 °C to 24 °C, and would cause oxyhaemoglobin to dissociate, releasing oxygen, but no more than 20 ml per litre of blood. Measuring error has been calculated at ± 3 ml min^{-1}, and the *in vitro* test showed a discrepancy between calculated and measured gas exchange, probably because of large temperature differentials within the oxygenator, and it can only be assumed that these factors were responsible for the output of oxygen. This view is supported by the fact that gas exchange at the end of 60 min equilibration in patient 4 was within the calculated error range of ± 3 ml min^{-1}.

Sudden fluctuations in $\dot{V}O_2$ and $\dot{V}CO_2$ were found as soon as bypass commenced and could have been caused by surges in the gas space of the oxygenator reservoir and marked temperature differentials. It is unlikely that they were caused by gas exchange through the lungs, since ventilation was stopped as soon as bypass commenced, except in patient 3, who showed considerable fluctuations during the initial period of partial bypass. Argon was used as the inert tracer gas and, since it has a temperature solubility coefficient similar to that of oxygen, this effect would counteract the effect of temperature solubility with respect to oxygen, and be negligible for carbon dioxide, which is 30 times more soluble. Therefore, in relation to temperature, the carbon dioxide changes indicate both the metabolic and solubility effects, whilst oxygen changes probably represent only the metabolic effect.

Patient 1 (15% carbon dioxide), in whom the temperature was maintained stable at 35 °C, showed stabilization of oxygen uptake at normal values within 10–15 min, but carbon dioxide showed an exponential uptake as would be expected when a patient who was normocarbic was exposed to 15% carbon dioxide. After about 20 min carbon dioxide also stabilized at an output equivalent to normal, which gave a ratio $\dot{V}CO_2 : \dot{V}O_2{}^1 = 0.8$. When this ratio returned to normal, solubility equilibrium had been reached. Patient 2 (15% carbon dioxide, hypothermia) also showed a sudden rapid uptake of carbon dioxide at the commencement of bypass. However, unlike patient 1, in whom the carbon dioxide output reached stability after 20 min, patient 2 showed a continuing carbon dioxide uptake during the whole 30-min period of temperature stability at 22 °C. Only during rewarming was there a carbon dioxide output, and RQ approached 0.7. This demonstrates that sudden cooling greatly prolongs the period of time required for equilibration of the body tissues with carbon dioxide in the blood in the oxygenator. It can be predicted that, if 5% carbon dioxide is used during rapid cooling, the body tissue carbon dioxide tension will remain less than the pre-cooling value for more than 30 min. This is demonstrated by patient 3 (5% carbon dioxide) who, during sudden cooling, showed a marked reduction in the output of carbon dioxide, RQ 0.1, followed by a gradual increase towards normal during the 30-min period of stable temperature at 21.5 °C, only reaching RQ 0.7 immediately before rewarming. Therefore, during rapid cooling, unless the carbon dioxide concentration of the input to the oxygenator is increased, there will inevitably be a decrease in $P\text{CO}_2$ in the patient. Our results suggest that the concentration of carbon dioxide should be substantially greater than 5% during rapid cooling, but probably less than 15%.

The fourth patient underwent a period of circulatory arrest of 60 min at a temperature of 21 °C (oesophageal). Upon recirculation at 21 °C constant temperature, there was an immediate large uptake of oxygen which declined over 10 min from 12 ml min^{-1} at 23 °C, or 1.2 ml $\text{kg}^{-1}\,\text{min}^{-1}$ (calculated value at 23 °C would be 1.8 ml $\text{kg}^{-1}\,\text{min}^{-1}$). As had been suggested (Abbott, 1977), this initial great uptake of oxygen was associated with a large output of carbon dioxide. The total amount of carbon dioxide given off during the period of recirculation and rewarming after circulatory arrest was proportionately greater than the uptake of oxygen during this time, although the rate of output reached normal values after complete rewarming to 36 °C, when RQ was 0.86. The larger carbon dioxide output probably arose from two sources. It has been postulated that, during circulatory arrest, aerobic metabolism continues at reduced rates because of hypothermia, producing carbon dioxide, until tissue oxygen stores are depleted, and then aerobic metabolism continues, also at reduced rate, producing lactic and pyruvic acid. This metabolic acidosis will result in an increase in dissolved carbon dioxide. Therefore, on reperfusion following circulatory arrest, the extra carbon dioxide would be washed out of the tissues.

The complex changes which occur in acid–base balance in hypothermia have been fully reviewed by Brooks (1962, 1964), who showed that widely differing pH values can be obtained, depending on the method of producing hypothermia—for example pump-oxygenator cooling or surface cooling or both—and also on the method of blood-gas measurement and whether temperature correction factors are applied. The present study has shown that continuous monitoring of $\dot{V}\text{O}_2$ and $\dot{V}\text{CO}_2$ during cardiopulmonary bypass and hypothermia can provide important information about the rate at which these indices are changing, and also indicate when stability of gas exchange has occurred following a sudden change in body temperature. Although the technique used in this study required complex technical back-up in order to interpret the signals from the mass-spectrometer, and in so doing resulted in the information being available only retrospectively, it should be possible to develop the method to provide $\dot{V}\text{O}_2$, $\dot{V}\text{CO}_2$ on a continuous real-time basis. This information would be useful in the clinical management of patients undergoing cardiopulmonary bypass and hypothermia.

ACKNOWLEDGEMENTS

Dr G. Clark was a Research Fellow funded by the National Heart Research Fund. We also wish to acknowledge financial assistance given by the locally constituted Research Committee of the Merseyside Regional Health Authority.

REFERENCES

Abbott, T. R. (1977). Oxygen uptake following deep hypothermia. *Anaesthesia*, **32**, 524.

Bjork, V. O., and Holmdahl, M. H. (1961). The oxygen consumption in man under deep hypothermia and the safe period of circulatory arrest. *J. Thorac. Cardiovasc. Surg.*, **42**, 392.

Brooks, D. K. (1962). Acid–base balance in hypothermia; in *Modern Trends in Anaesthesia* (eds F. T. Evans and T. C. Gray), No. 2, Ch. 5, p. 102. London: Butterworths.

Brooks, D. K. (1964). The meaning of pH at low temperatures during extracorporeal circulation. *Anaesthesia*, **19**, 337.

Brown, B., and Sellick, B. A. (1965). Controlled hypothermia in open-heart surgery under hypothermia. *Lancet*, **2**, 452.

Burton, G. W. (1964). Metabolic acidosis during profound hypothermia. *Anaesthesia*, **19**, 365.

Callaghan, P. B., Lister, J., Paton, B. S., and Swan, H. (1961). Effect of varying carbon dioxide tensions on the oxyhaemoglobin dissociation curve under hypothermic conditions. *Ann. Surg.*, **154**, 903.

Clowes, G. H., Neville, W. E., Sabga, G., and Shibota, Y. (1958). The relationship of oxygen consumption, perfusion rate and temperature to the acidosis associated with cardiopulmonary bypass. *Surgery*, **44**, 220.

Goodwin, B. (1978). Sources of error in mass spectrometry; in *Medical and Biological Applications of Mass Spectrometry* (eds J. P. Payne, J. A. Bushman and C. W. Hill). London: Academic Press.

—— Holme, A. E., and Leck, J. H. (1977). The performance of a simple respiratory gas analyser using a quadrupole mass spectrometer. *Proc. 7th Int. Vacuum Congr. and 3rd Int. Conf. on Solid Surfaces*, Vienna, 1977.

Harris, E. A. (1973). Metabolic aspects of profound hypothermia; in *Heart Disease in Infancy: Diagnosis and Surgical Treatment* (eds B. G. Barratt-Boyes, J. M. Neutze and E. A. Harris), p. 65. Edinburgh: Churchill Livingstone.

Johnston, A. E., Radde, I. C., Steward, D. J., and Taylor, J. (1974). Acid–base and electrolyte changes in infants undergoing profound hypothermia for surgical correction of congenital heart defects. *Can. Anaesth. Soc. J.*, **21**, 23.

Lunding, M., and Rygg, I. H. (1968). Evaluation of the sufficiency of tissue oxygenation during cardiopulmonary bypass and hypothermia using the Rygg/Kyvsgaard pump oxygenator. *Scand. J. Thorac. Cardiovasc. Surg.*, **2**, 169.

Severinghaus, J. W., Ozanne, G. M., and Lauderbough, H. (1978). Measurement of lung weight and cardiac output with a mass spectrometer. *Acta Anaesthesiol. Scand.*, (Suppl. 70), 161.

Starr, A. (1959). Oxygen consumption during cardiopulmonary bypass. *J. Thorac. Cardiovasc. Surg.*, **38**, 46.

Zeidifard, E., Godfrey, S., and Davies, E. E. (1976). Estimation of cardiac output by an N_2O rebreathing method in adults and children. *J. Appl. Physiol.*, **41**, 433.

MESURE A L'AIDE D'UN SPECTROMETRE DE MASSE DE L'ABSORPTION D'OXYGENE ET DE L'ECHANGE DE GAZ CARBONIQUE PENDANT UNE DERIVATION CARDIOPULMONAIRE

RESUME

On a mesuré en continu sur quatre enfants pendant une dérivation cardiopulmonaire l'absorption d'oxygène ($\dot{V}O_2$) et la production de gaz carbonique ($\dot{V}CO_2$), en utilisant les variations de concentration de l'argon, gaz traceur, comme mesure du débit, ainsi qu'un spectromètre de masse pour surveiller les concentrations de gaz. Les valeurs normales du rapport de $\dot{V}CO_2 : \dot{V}O_2$ ($=0,8$) indiquent que l'equilibre de l'échange de gaz s'est établi après des changements soudains dans la température du corps. Pendant le refroidissement rapide, il faut 10% de gaz carbonique pour assurer l'homéostase du gaz carbonique à l'intérieur du corps.

MASSENSPEKTROMETERMESSUNG DER SAUERSTOFFAUFNAHME UND DES KOHLENDIOXYD-AUSTAUSCHES BEI HERZ-LUNGEN-BYPASS

ZUSAMMENFASSUNG

Sauerstoffaufnahme ($\dot{V}O_2$) und Kohlendioxydabgabe ($\dot{V}CO_2$) wurden kontinuierlich bei vier Kindern während Herz-Lungen-Bypass gemessen, unter Verwendung der Konzentrationsvariation des Spurengases Argon zur Durchflussmessung, und eines Massenspektrometers für die Gaskonzentrationen. Die normalen Werte für das Verhältnis $\dot{V}CO_2 : \dot{V}O_2$ ($=0,8$) zeigen, dass ein Gasaustausch-Gleichgewicht nach den plotzlichen Änderungen der Korpertemperatur geschaffen wurde. Während rascher Abkühlung 10% Kohlendioxyd erforderlich, um die Kohlendioxyd-Homoostase im Korper zu gewahrleisten.

MEDICION POR ESPECTOMETRO DE MASA DE LA CAPTACION DE OXIGENO E INTERCAMBIO DE BIOXIDO DE CARBONO DURANTE DESVIACION CARDIOPULMONAR

SUMARIO

Se llevaron a cabo mediciones de la captación de oxígeno ($\dot{V}O_2$) y de la producción de bióxido de carbono ($\dot{V}CO_2$) en una base permanente en cuatro niños sometidos a desviación cardiopulmonar, mediante el uso de la variación en la concentración de un gas indicator, argón, como medida del flujo y de un espectómetro de masa para controlar las concentraciones de gas. Los valores normales para la relación de $\dot{V}CO_2 : \dot{V}O_2$ ($=0,8$) demuestran que el equilibrio del intercambio de los gases se estableció a raíz de los cambios repentinos de la temperatura del cuerpo. En el curso de un enfriamiento rápido, se necesita un 10% de bióxido de carbono para asegurar la homeostásis del bióxido de carbono dentro del cuerpo.

Br. J. Anaesth. (1980), **52**, 41

RADIAL ARTERY CANNULATION

A prospective study in patients undergoing cardiothoracic surgery

F. M. Davis and J. M. Stewart

SUMMARY

Following 333 radial artery cannulations, the frequency of complete occlusion of the vessel on the day after removal of the cannula was 30%, decreasing to 24% by the 8th day. Arterial occlusion was assessed using a modified Allen's test and an ultrasonic flow meter. The frequency correlated with the type and size of cannula used, being least (3%) with 20-gauge Teflon cannulae, with the degree of bruising, and with the sex of the patient, being significantly greater in women (37.5%) than in men (27%). Other variables such as insertion technique, low cardiac output, anticoagulation after operation and the duration of cannulation were assessed. Using multivariate analysis of 13 variables, it did not appear possible to predict with any certainty the outcome of arterial cannulation. The frequency of major complications was small and no permanent sequelae were detected.

Percutaneous radial artery cannulation is a well-established clinical technique. Several large retrospective reviews (Mortensen, 1967; Zorab, 1969; Dalton and Laver, 1971; Gardner et al., 1974) have suggested that serious complications such as gangrene of the extremities have been rare, although there is a definite morbidity, in particular the occurrence of thrombosis and occlusion. Recently, Bedford (1977) and Davis (1978) have reported that the type and size of catheter employed significantly influences the frequency of subsequent thrombosis. The importance of possible "risk" factors and their predictive value in the development of arterial thrombosis is reviewed.

METHODS

Three hundred and thirty-three radial artery cannulations were performed in 330 adult patients over an 8-month period, all except 11 undergoing cardiopulmonary bypass surgery with moderate (30–32 °C) hypothermia (table I).

There are inevitable differences between the surgical groups. Only 15% of procedures performed in patients aged less than 40 yr were coronary artery bypass grafts (CABG), whereas by the sixth decade CABG accounted for 80% and were more often performed in men (63%) than in women (30%). On the other hand, 74% of all mitral valve surgery was performed in women, whilst aortic valve surgery was distributed proportionately in the two sexes. These differences may be relevant to subsequent discussion regarding the frequency of radial artery thrombosis.

The first phase of the study was an assessment of current departmental practice. The second phase was a randomized trial of four cannulae to assess the influence of catheter size and material on arterial occlusion (Davis, 1978). For the purposes of this report the data from these two phases have been combined, there being no statistically significant differences in the cannula groups common to both—18- and 20-gauge polypropylene catheters.

Assessment before operation

Collateral arterial blood supply to the hand was assessed using the modified Allen's test (Allen, 1929; Oh and Davis, 1975). This was graded as: grade 1,

Table I. *The distribution of patients with regard to sex and nature of surgery (no data for five patients); mean age* 50.8 yr (*range* 12–85 yr); *overall hospital mortality* 3.3%

	Male	Female	Total
Coronary artery bypass grafts (13 plus other surgery)	155	24	179
Aortic valve replacement (all homografts except six)	56	15	71
Mitral valvotomy/replacement Multiple valve replacement	16	33	49
Miscellaneous (LV and aortic aneurysm, congenital defects, arch reconstructions, etc.)	17	9	26
Total	244	81	325

F. M. Davis,* m.a., m.b., b.chir., f.f.a.r.c.s., Department of Cardiothoracic Anaesthesia, Green Lane Hospital, Auckland, New Zealand. Joanna M. Stewart, m.sc., Christchurch Clinical School, Christchurch, New Zealand.

* Present address for correspondence: Christchurch Public Hospital, Christchurch 1, New Zealand.

0007-0912/80/010041-07 $01.00

© Macmillan Journals Ltd 1980

0–7 s "flush" time, normal; grade 2, 8–14 s, equivocal; grade 3, longer than 15 s, poor or abnormal. In some patients, arterial dominance was noted (Husum and Palm, 1978).

Cannulation technique

Cannulation was performed using a single-wall puncture or transfixion of the artery either percutaneously (299 patients) or via a surgical cut-down. The cannula was flushed intermittently with a few millilitre of 5% dextrose solution containing heparin 2500 i.u. per 500 ml. A continuous flushing device was not used in this study. Four different cannulae were used: 18- and 20- gauge polypropylene (Argyle Medicut), and 18- and 20-gauge Teflon (Longdwell) catheters.

Post-cannulation examination

Patients were examined on several occasions by one person (FMD) following removal of the cannulae, the examiner being unaware of the catheter used. Assessment involved inspection of the puncture site and hand, palpation of the distal radial pulse, Allen's test and the use of an ultrasonic flow probe.

Inspection. The presence of discharge or inflammation was recorded. Haematoma was scored 0 (no bruising) to 4 (severe bruising reaching to the elbow, plus considerable local swelling). Evidence of impaired blood supply, particularly over the radial aspect, and swelling of the hand were noted.

Radial pulse. The strength of the radial pulse distal to the puncture site was recorded as normal, that is equal to the non-cannulated side, reduced or absent.

Allen's test. This was graded as described above. Whilst the preoperative grade referred to the ulnar release "flush" time, after the catheter's removal the "flush" time from the radial artery was recorded.

Palmar blood flow. A Doppler flow meter (Sonicaid Foetal Heart Monitor) placed on the thenar eminence of the palm as described by Mozersky and others (1973) was used. Patency of the radial artery was graded in three categories by the combined use of Allen's test and flow monitoring with the ulnar artery compressed: *Normal*—grade 1 or 2 Allen's test plus a "normal" biphasic flow signal. *Partial occlusion*—grade 2 or 3 Allen's test plus a reduced uniphasic flow signal which did not completely disappear with ulnar compression. *Complete occlusion*—grade 3 Allen's test plus a reduced uniphasic flow signal which disappeared completely with ulnar compression.

Grade 1 Allen's test was never associated with an impaired flow signal, but a "normal" biphasic signal was occasionally heard in combination with a grade 2 Allen's test.

Thumb temperature. The skin temperature of both thumbs was measured in 78 patients using a YSI Telethermometer and series 400 skin probe.

Statistics

Data retrieval was over 80% for all variables. Univariate analysis of the raw data utilized routine statistical tests, namely, the χ^2 test, Fisher's exact test, Dunn's test for Multiple Comparisons (Dunn, 1964), Mann–Whitney *U* Test (*Z* statistic) and Kruskal–Wallis one-way analysis of variance (*H* statistic). A 2% level of significance was used throughout.

In an attempt to discover how accurately the recorded variables could predict the likelihood of thrombosis and which variables appeared to be important in doing so, the multivariate successive screening technique was used. The 13 independent variables that it was hoped might be useful in predicting the probability of thrombosis were: age, sex, surgical procedure, cannula type, cannula size, number of attempts at arterial puncture, the actual number of vessel punctures, repeat cannulation, cut-down procedure, time catheter left *in situ*, low cardiac output state, size of haematoma and use of anticoagulants. The three categories formed from the Allen's test and Doppler flow monitoring were used as the groups to which it was attempted to allocate the patients using the above variables. Only those patients with all these variables recorded were included.

As the independent variables were mainly categorical in nature, the usual discriminant function techniques could not be used. Therefore, a sequential screening approach (Fieldman, Klein and Honigfeld, 1969, 1972) which makes no distribution assumptions was used. At each step of this technique the item which maximizes the ratio of true to false positives is accepted and the patients satisfying this criteria are classified. Eventually, this results in all patients being classified into the three groups.

RESULTS

Allen's test before operation

Eighty per cent of patients had good ulnar collateral flow. In 17% collateral flow was present but diminished and it was absent in 3% of patients, bilaterally absent in three. There was no difference between the sexes. In 26 patients who had undergone cardiac surgery previously, radial blood flow appeared normal before operation. However, in three a stricture of the vessel was apparent during cannulation.

Frequency of thrombosis

Complete occlusion of the radial artery occurred in 30% of patients one day after removal of the cannula, reducing to 24% by the 8th day. A further 12% were partially occluded. The frequency of occlusion using the four different cannulae varied ($H = 19.9$; 3 d.f.); the 20-gauge Teflon cannula having a significantly lesser frequency (3%) than the other three used (fig. 1).

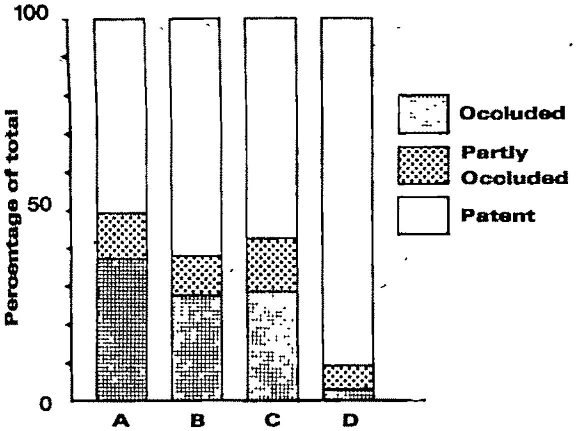


FIG. 1. The frequency of partial or complete radial artery occlusion (expressed as a percentage) following the use of four different cannulae. Group A: 18-gauge polypropylene ($n = 166$); B: 20-gauge polypropylene ($n = 92$); C: 18-gauge Teflon ($n = 41$); D: 20-gauge Teflon ($n = 34$) catheters.

To examine related aspects of arterial occlusion the data for all cannula groups were combined, the only significant difference between them being a preponderance of women in the 20-gauge Teflon group ($\chi^2 = 13.3$; 3 d.f. — see below). Results for the 1st and 8th days following catheter removal were essentially similar unless specifically stated.

Significant associations were found between occlusion and the following variables:

Sex. Occlusion occurred more frequently in women than in men (table II). This is of importance in the analysis of the four types of cannula used, as the group with the lowest rate of occlusion—20-gauge Teflon—contained a significantly higher proportion of women than did the others.

TABLE II. *The frequency of radial artery occlusion was significantly greater in women than in men* (*Z statistic shown*)

	Number of patients			
	Day 1		Day 8	
	Male	Female	Male	Female
Patent	146	38	161	42
Partial occlusion	24	12	22	12
Complete occlusion	62	30	49	26
	$Z = 2.3$		$Z = 2.8$	

Number of arterial punctures. Forty-seven and a half per cent of vessels were occluded following multiple punctures during cannulation, compared with 26% when only a single insertion was made ($H = 9.8$; 2 d.f.).

Surgical cut-down. This was performed in 34 patients. The frequency of occlusion on the first day was greater (48%) than for percutaneous cannulation (23%); $Z = 3.0$. By the end of 1 week there was no longer a significant difference between the two techniques.

Low cardiac output. In 53 patients who had a low cardiac output after surgery, most of whom received positive inotropic agents, the frequency of occlusion was significantly greater (44%) than in those who followed a "normal" course after operation (25%); $Z = 2.8$. The only two cases of severe hand ischaemia in this series occurred in patients with prolonged low output states over many days.

Surgical procedure. Because of the varied nature of the surgery undertaken it proved difficult to assess this factor and no definite conclusions can be drawn. Certainly, statistical differences in the frequency of occlusion occurred, but these cannot be separated easily from other related factors.

Anticoagulation after operation. Two methods of anticoagulation were used. In patients undergoing CABG, subcutaneous low-dose heparin was commenced 6 h after removal of chest drains, while warfarin sodium was prescribed after prosthetic valve replacements and some mitral valvotomies. Patients receiving an aortic homograft valve were not anticoagulated. The 1st-day examination occurred before anticoagulation in most cases and there were no statistical differences between these three groups of patients. However, by the 8th day there was a greater frequency of occlusion in those patients receiving warfarin (48%) than either those receiving subcutaneous heparin (20%) or those receiving no anticoagulants (22%) (table III).

TABLE III. *The frequency of radial artery occlusion was significantly greater in patients anticoagulated with warfarin after operation than in those treated with subcutaneous low-dose heparin or not receiving anticoagulants (H statistic shown)*

	Number of patients		
	No anti-coagulation	Heparin	Warfarin
Patent	56	138	19
Partial occlusion	13	18	3
Complete occlusion	19	39	20
	$H = 12.3$; 2 d.f.		

Haematoma formation. Occlusion occurred in 14 of 29 (48%) patients with a large haematoma compared with only 23% in those with minimal or no bruising. Large bruises were more common in women than in men ($Z = 3.0$), after cut-down procedures ($Z = 2.8$), and after anticoagulation with warfarin ($H = 12.6$; 2 d.f.).

Non-significant variables. No statistical association was found between the frequency of arterial occlusion and age, previous cannulation of the same vessel, Allen's test before operation or the technique of cannulation (single-wall or transfixion). The mean duration of cannulation was 27 h with a range of 1–80 h. The frequency of occlusion did not increase with the duration of cannulation. No occlusions were seen following cannulation of less than 4 h. Bacterial cultures were possible from 24 of 59 cannula tips using an enrichment media technique (Davis and Cornere, 1979), but the occurrence of infection was not significantly associated with the occlusion rate ($\chi^2 = 2.099$; 1 d.f.).

Predictability of thrombosis

The results for multivariate analysis using the sequential screening method on the 1st day after removal of the catheter are shown in table IV. Only 32% of category 3 patients were correctly classified by this technique, 23% of category 2 and 91% of category 1. The results for the 8th day were similar. The outcome of this analysis would appear to be rather unsatisfactory as a means of predicting the patient likely to develop thrombosis. Thus, although many of the variables investigated correlated with the likelihood of thrombus formation, they do not, on their own, predict the outcome. For both the 1st and 8th days, cannula type and size and the grade of haematoma were the variables which best separated the groups. The sex of the patient was also of importance on the 8th day.

TABLE IV. *Prediction of occlusion with the sequential screening technique utilizing* 13 *variables or "risk" factors*

	Classification according to screening technique			
	1	2	3	Total
Clinical classification				
1 Normal	147	4	11	162
2 Partial occlusion	23	7	1	31
3 Complete occlusion	43	9	24	76
Total	213	20	36	269

Features associated with thrombosis

Cannula management. Pressure waveform damping or difficulty in drawing blood samples soon negate the value of an arterial line. These were encountered in 30% of patients; twice as often in those patients whose arteries subsequently occluded than in those patients with patent vessels (table V).

TABLE V. *Damping of the pressure wave-form or difficulties withdrawing blood samples occurred more often in patients whose radial artery was subsequently found to be thrombosed (Z statistic shown)*

	Number of patients	
	Difficulties with monitoring or sampling	No difficulties
Patent	29	151
Partial occlusion	11	22
Complete occlusion	41	49
	$Z = 5.2$	

Distal radial pulse. The radial pulse was palpable distally in 49% of completely occluded vessels, and in 7% was equal in volume to the pulse on the opposite, non-occluded side.

Thumb skin temperature. There was only a small non-significant difference in temperature between the two sides (−0.76 °C, range −4.5 °C to +3.2 °C; $H = 6.1$; 2 d.f.).

Clinical sequelae

Twelve patients (3.6%) developed signs of impaired perfusion of the hand during or following cannulation. In only two elderly women who developed prolonged low cardiac output following mitral valve replacement did this last longer than 1 day. One required repeated sympathetic blockade (axillary brachial plexus block) to treat gangrene of her hand which eventually recovered.

Transient numbness of the thumb occurred in one case.

Superficial inflammation of the skin entry site was seen after eight percutaneous (2.7%) and eight cut-down (23.5%) cannulations. Bacterial cultures were negative in these, and the inflammation settled rapidly.

Accidental removal of the cannula (two patients) and disconnection of the manometer line (two patients) were the only technical complications encountered.

DISCUSSION

There is evidence that both the type and size of cannula used are of importance in reducing the risks of arterial occlusion (Downs et al., 1973; Bedford, 1975, 1977; Kim, Arakawa and Bliss, 1975), but not all studies have supported this (Bedford and Wollman, 1973; Evans and Kerr, 1974). The present study confirms that occlusion is greatly minimized by using 20-gauge Teflon cannulae. Thus, the high frequency of complications, especially hand ischaemia, reported using 15-gauge catheters (Little, Clarke and Shanks, 1975) can be readily avoided.

Our findings substantiate that occlusion occurs more commonly in women than in men (Kim, Arakawa and Bliss, 1975). This is most likely to be related to the ratio of the lumen of the vessel to the external diameter of the catheter as reported by Bedford (1977). One might predict, therefore, a higher frequency of occlusion in children even if 22-gauge Teflon catheters are used.

The dynamics of blood flow have been reported in only 12 patients (Ryan et al., 1973). The effect of pre-existing arterial disease has not been elucidated, although diminished digital pulse volume has been reported by Ryan in five of seven patients with previous brachial artery catheterization. Re-cannulation of 26 previously cannulated vessels in our patients, however, did not appear to result in an increased frequency of occlusion or hand ischaemia.

It was further suggested by Ryan and others (1973) that the non-dominant artery should always be cannulated in preference. This is probably unnecessary, provided the collateral flow from the other vessel is adequate. Indeed, there was evidence from the 46 patients in whom we assessed arterial dominance to suggest that partial or complete occlusion was significantly more likely to occur if the radial artery were the non-dominant vessel ($H = 8.2$; 2 d.f.). This observation, which requires to be confirmed, may be related to the findings of Bedford (1977). Cannulation of 33 radial arteries in the face of a grade 2 Allen's test was uneventful, and this level of ulnar collateral flow can probably be regarded as acceptable. Bedford (1977) has adopted the more stringent criteria of a thenar eminence "flush" within 5 s of ulnar release.

Increased trauma to the vessel because of multiple needling or surgery does seem to increase the likelihood of subsequent occlusion, although others have not been able to demonstrate this (Kim, Arakawa and Bliss, 1975). It is important to note that not all surgical cut-downs thrombose. Therefore, routine ligation of the vessel distally cannot be condoned, and cannulation is best performed by single-wall puncture using trocar and 20-gauge cannula under direct vision when a cut-down is necessary.

The frequency of thrombosis has been reported to be related to the duration of cannulation (Bedford and Wollman, 1973; Evans and Kerr, 1974), but others have been unable to confirm this (Kim, Arakawa and Bliss, 1975). In the present study, there was no relationship between the duration of cannulation and the frequency of occlusion. However, there were only 12 patients in our series in what appears to be the critical 6–18-h cannulation period (Bedford and Wollman, 1973).

We were able to confirm the observations of Gardner and others (1974) that arterial complications are more common in the presence of hypotension and following the use of inotropic agents. However, the value of an intra-arterial line in such life-threatening circumstances outweighs the risks of local vascular complications. No permanent sequelae were observed in the present series, nor was any surgical intervention required.

Thermographic differences have been reported between the upper limbs of patients with clinically demonstrable arterial occlusion (Evans and Kerr, 1974). However, thumb temperature difference between the two sides did not appear to be a particularly useful screening test for occlusion in the present study. The presence of venous cannulae and subsequent common occurrence of superficial venous thrombosis in the same limb may have contributed to this. We have reported a much greater frequency of damping and sampling problems in vessels which were subsequently shown to be occluded. The occurrence of these difficulties during cannulation should raise suspicion of the development of an arterial thrombosis.

From our studies, it does not appear possible to state the probability of subsequent radial artery thrombosis with accuracy, although many "risk" factors contribute to the morbidity of the technique. Therefore, guidelines for patient care (Oh and Davis, 1975) should be followed in order to minimize complications. In particular, the duration of cannulation should be the shortest and the Teflon cannula the smallest compatible with clinical needs.

The most important factors related to occlusion following arterial cannulation are the size and material of the catheter. The frequency reported with 20-gauge Teflon cannulae was only 3%. Secondarily, the patient's sex, trauma to the vessel, low cardiac output states and aspects of general patient care and catheter management all play a part. It does not appear possible from our data to predict the outcome of arterial cannulation in any given patient on the basis of these variables. The frequency of major complications was extremely low, and without permanent sequelae. The risks of arterial occlusion must be weighed against the proven value of direct intra-arterial pressure monitoring and serial arterial blood sampling.

ACKNOWLEDGEMENTS

The assistance of all nursing and anaesthetic colleagues in the Cardio-Thoracic Surgical Unit, Green Lane Hospital, Auckland, was appreciated. We wish to thank the surgical staff for permission to study patients under their care. Dr Davis is particularly indebted to Dr Eve Seelye for her advice and encouragement.

REFERENCES

Allen, E. V. (1929). Thromboangiitis obliterans. Methods of diagnosis of chronic occlusive arterial lesions distal to the wrist with illustrative cases. *Am. J. Med. Sci.*, **178**, 237.

Bedford, R. F. (1975). Percutaneous radial artery cannulation: increased safety using Teflon catheters. *Anesthesiology*, **42**, 219.

—— (1977). Radial artery function following percutaneous cannulation with 18- and 20-gauge catheters. *Anesthesiology*, **47**, 37.

—— Wollman, H. (1973). Complications of percutaneous radial artery cannulation: an objective prospective study in man. *Anesthesiology*, **38**, 228.

Dalton, B., and Laver, M. B. (1971). Vasospasm with an indwelling radial artery cannula. *Anesthesiology*, **35**, 194.

Davis, F. M. (1978). Radial artery cannulation: influence of catheter size and material on arterial occlusion. *Anaesth. Intens. Care*, **6**, 49.

—— Cornere, B. (1979). Bacterial contamination of radial artery catheters. *N.Z. Med. J.*, **89**, 128.

Downs, J. B., Rackstein, A. D., Klein, E. F., and Hawkins, I. F. (1973). Hazards of radial artery catheterisation. *Anesthesiology*, **38**, 283.

Dunn, O. J. (1964). Multiple comparisons using rank sums. *Technometrics*, **6**, 241.

Evans, P. J. D., and Kerr, J. H. (1974). Complications of arterial cannulation and thermographic assessment of sequelae. *Br. J. Anaesth.*, **46**, 318.

Fieldman, S., Klein, D. F., and Honigfeld, G. (1969). A comparison of successive screening and discriminant function techniques in medical taxonomy. *Biometrics*, **25**, 725.

—— —— —— (1972). The reliability of a decision tree technique applied to psychiatric diagnosis. *Biometrics*, **28**, 831.

Gardner, R. M., Schwartz, R., Wong, H. C., and Burke, J. P. (1974). Percutaneous indwelling radial-artery catheters for monitoring cardiovascular function. *N. Engl. J. Med.*, **290**, 1227.

Husum, B., and Palm, T. (1978). Arterial dominance in the hand. *Br. J. Anaesth.*, **50**, 913.

Kim, J. N., Arakawa, K., and Bliss, J. (1975). Arterial cannulation. Factors in the development of occlusion. *Anesth. Analg.* (*Cleve.*), **54**, 836.

Little, J. M., Clarke, B., and Shanks, C. (1975). Effects of radial artery cannulation. *Med. J. Aust.*, **2**, 791.

Mortensen, J. D. (1967). Clinical sequelae from arterial needle puncture, cannulation and incision. *Circulation*, **35**, 1118.

Mozersky, D. J., Buckley, C. J., Hagood, C. O., Capps, W. F., and Dannemiller, F. J. (1973). Ultrasonic evaluation of the palmar circulation. A useful adjunct to radial artery cannulation. *Am. J. Surg.*, **126**, 810.

Oh, T. E., and Davis, N. J. (1975). Radial artery cannulation. *Anaesth. Intens. Care*, **3**, 12.

Ryan, J. F., Raines, J., Dalton, B., and Mathieu, A. (1973). Arterial dynamics of radial artery cannulation. *Anesth. Analg.* (*Cleve.*), **52**, 1016.

Zorab, J. S. M. (1969). Continuous display of the arterial pressure. *Anaesthesia*, **24**, 431.

POSE D'UNE CANULE DANS L'ARTERE RADIALE

Etude sur des patients subissant une intervention chirurgicale cardiothoracique

RESUME

Après avoir effectué 333 poses de canules dans l'artère radiale, la fréquence d'occlusion complète du vaisseau le lendemain du retrait de la canule a été de 30%; diminuant à 24% vers le huitième jour. On a évalué l'occlusion artérielle en se servant d'un débitmètre ultrason modifié et en utilisant le test d'Allen. La fréquence a été fonction du type et de la dimension de la canule utilisée, la plus faible (3%) étant constatée avec les canules en Téflon d'un calibre de 20; du degré de contusions et du sexe du patient, celle-ci étant nettement plus élevée chez les femmes (37,5%) que chez les hommes (27%). On a estimé d'autres éléments variables, tels que la technique d'insertion, la faiblesse du débit cardiaque, l'anticoagulation après l'opération et la durée de la pose de la canule. En procédant à des analyses de 13 éléments variables, il n'a pas semblé possible de prédire avec certitude les résultats de la pose

des canules artérielles. La fréquence de complications importantes a été faible et l'on n'a pu détecter aucunes séquelles permanentes.

KANÜLENEINFÜHRUNG IN DIE RADIALARTERIE

Studie von Patienten bei Herz-Brustraumoperationen

ZUSAMMENFASSUNG

Nach 333 Kanüleneinführungen in die Radialarterie betrug die Häufigkeit eines kompletten arteriellen Verschlusses am Tag nach Entfernung der Kanule 30% sinkend auf 24% nach 8 Tagen. Arterieller Verschluss wurde durch einen modifizierten Allen-Test und einen Ultraschall-Durchflussmesser festgestellt. Die Häufigkeit korrelierte mit Art und Grösse der verwendeten Kanule, und war am niedrigsten mit Teflon-Kanülen von 20-gauge (3%), ferner mit dem Ausmass der Quetschungen und mit dem Geschlecht der Patienten, wobei die Häufigkeit bei Frauen wesentlich höher (37,5%) war als bei Männern (27%). Andere variable Faktoren wie die Einführungsmethode, niedriges Herzminutenvolumen, Gerinnungshemmung nach der Operation und Dauer der Kanüleneinführung wurden ebenfalls beurteilt. Mit mehrfach veränderlicher Analyse von 13 variablen Faktoren schien es nicht möglich, das Ergebnis arterieller Kanüleneinführung mit irgendeiner Sicherheit vorauszusagen. Die Häufigkeit grösserer Komplikationen war gering, und keine permanenten Nebenerscheinungen wurden entdeckt.

CANULACION DE LA ARTERIA RADIAL

Un estudio exploratorio en pacientes sometidos a cirujía cardiotorácica

SUMARIO

A raíz de 333 canulaciones de la arteria radial, se comprobó que la frecuencia de una oclusión completa del vaso al día siguiente de la remoción de la cánula era de 30% y había disminuido hasta un 24% 8 días después. Se evaluó la oclusión arterial mediante una prueba de Allen modificada y un medidor ultrasónico de flujo. Dicha frecuencia en relación con el tipo y tamaño de la cánula usada era menor (3%) con cánulas de Teflón de calibre 20, y con el grado de contusión y el sexo del paciente mucho mayor en mujeres (37,5%) que en los hombres (27%). Se evaluaron también otras variables tales como técnica de inserción, función cárdiaca baja, anticoagulación después de la operación y duración de canulación. Al hacer un análisis multivariado de 13 variables, no pareció posible predecir con alguna certeza el resultado de la canulación arterial. Fue baja la frecuencia de complicaciones mayores y no se descubrió ninguna secuela permanente.

Br. J. Anaesth. (1980), **52**, 49

COMPARISON OF THE EFFECTS OF SPINAL ANAESTHESIA AND GENERAL ANAESTHESIA ON POSTOPERATIVE OXYGENATION AND PERIOPERATIVE MORTALITY

P. J. McKenzie, H. Y. Wishart, K. M. S. Dewar, I. Gray and G. Smith

SUMMARY

One hundred patients presenting for surgical treatment of fractured neck of femur were allocated to receive either spinal (SAB) or general (GA) anaesthesia. Before operation, the mean Pa_{O_2} was 9.04 kPa. There was a significant decrease in Pa_{O_2} of 0.68 kPa in GA group at 1 h after operation, while blood-gas values were unchanged in SAB group. Eight patients (15.7%) in GA group and five patients (10.2%) in SAB group died within 4 weeks of surgery. The difference was not statistically significant.

Fracture of the femoral neck is associated with considerable morbidity and a mortality rate ranging from 8.7% to 23% (Allen and Metcalf, 1965; Aldrete, Davis and Hingson, 1967; Honkonen, Tarkkanen and Julkunen, 1971; Barnes et al., 1976; Gallannaugh, Martin and Millard, 1976; Martin, 1977). In addition, it is well known that arterial oxygenation decreases with increasing age, probably as a result of increasing maldistribution of ventilation/perfusion ratios (Gillies et al., 1977). Moreover, it has been suggested that patients with a fractured neck of femur have Pa_{O_2} values even smaller than would be predicted on the basis of age alone (Phillips and Tomlin, 1977).

While it is known that several general anaesthetic techniques cause a small but significant further deterioration in arterial oxygenation after operation (Wishart, Williams and Smith, 1977), spinal anaesthesia is thought to have little effect on arterial oxygen and carbon dioxide tensions (de Jong, 1965) and has been recommended for lower limb surgery in patients with impaired respiratory performance (Scott and Thorburn, 1975). In this study we have compared the effects of spinal and general anaesthesia on postoperative arterial oxygenation and mortality in two groups of patients undergoing surgical correction of fractured neck of femur.

PATIENTS AND METHODS

One hundred unselected patients presenting for internal fixation of fractured neck of femur were allocated randomly to receive either general anaesthesia (GA group) or spinal anaesthesia (SAB group). Surgery was usually performed within 1–3 days of admission, although two patients, one in each group, were delayed by 14 and 19 days respectively. Many of the patients suffered from other conditions common to their age group, including cardiovascular and respiratory disease, and diabetes. Patients requiring a Thompson prosthesis were excluded from the study as the insertion of the prosthesis and cement may produce a decrease in arterial pressure and Po_2 (Modig et al., 1975).

None of the patients received premedication. An i.v. infusion of crystalloid solution was given to each patient for 12–24 h before operation to minimize the dehydration which occurs commonly in this type of elderly patient. Surgery comprised the insertion of either a J.T.B. nail-plate, a Honey–Capener nail-plate or a K.Y. nail.

GA group

Fifty-one patients received general anaesthesia induced with Althesin 1.0–3.0 ml. Following the administration of suxamethonium 50 mg, the trachea was intubated with a cuffed tube. Anaesthesia was maintained with 66% nitrous oxide and 0.75–1.25% halothane in oxygen. The patients breathed spontaneously via a semi-closed breathing system, with

---

P. J. McKenzie, F.F.A.R.C.S.; H. Y. Wishart, F.F.A.R.C.S.; K. M. S. Dewar, F.F.A.R.C.S.; Division of Anaesthesia, Western Infirmary, Glasgow, G11 6NT. I. Gray, F.R.C.S., Department of Orthopaedic Surgery, Western Infirmary, Glasgow, G11 6NT. G. Smith,* M.D., F.F.A.R.C.S., University Department of Anaesthesia, Western Infirmary, Glasgow, G11 6NT.

* Present address: Department of Anaesthetics, The General Hospital, Gwendolen Road, Leicester LE5 4PW.

0007-0912/80/010049-06 $01.00

© Macmillan Journals Ltd 1980

carbon dioxide absorption, with a fresh gas flow of 3 litre min^{-1}.

SAB group

Forty-nine patients received 1.3–1.5 ml of hyperbaric cinchocaine 0.5% ("heavy nupercaine") injected slowly (without barbotage) into the subarachnoid space via a 22-gauge needle. The block was performed with the patient in the horizontal and lateral position and the fractured hip dependent. Discomfort caused by turning to this position was transient and minimized by gentle handling. After injection, the patient was turned to the supine position and remained horizontal. Nine patients received sedation with small doses of diazepam i.v. One patient received metoclopramide (Maxolon) for nausea.

In both groups arterial blood samples were withdrawn into heparinized plastic syringes from the radial artery of the supine patient before the induction of anaesthesia, 1 h after induction and 1 h after the end of anaesthesia. When oxygen therapy was given in the period after operation, this was discontinued (if considered safe to do so) and the patient breathed room air for at least 20 min before the arterial blood sample was withdrawn. Two patients in the GA group were considered too unwell to permit the discontinuation of oxygen therapy. These samples were analysed immediately for Pa_{O_2}, Pa_{CO_2}, pH and base excess using a Radiometer ABL 1 automated blood-gas analyser.

Corrections were applied for the difference between the temperature of the electrodes and the patient's temperature.

RESULTS

There were no significant differences between the groups in respect of age, sex distribution, duration of surgery, blood loss at operation, volume of fluid infused or the interval between admission to hospital and time of surgery (table I). Both groups showed a similar decrease in temperature following surgery. In GA group, two patients required blood transfusion during operation. Blood transfusion was not required in SAB group. All patients received an infusion of crystalloid and seven patients in each group received, in addition, an infusion of plasma protein solution or plasma expander.

There was a significantly greater decrease in systolic arterial pressure in SAB group (table II) (mean decrease 64 mm Hg) compared with GA group (45 mm Hg).

TABLE I. *General details of patients studied (mean ± SEM)*

	GA group	SAB group
Number	51	49
Age (yr)	74.5 ± 2.29	76.8 ± 1.38
Axillary temperature (°C)		
Before operation	36.7 ± 0.088	36.7 ± 0.08
After operation	36.02 ± 0.10	36.1 ± 0.112
Duration of surgery (min)	76.5 ± 3.99	77.8 ± 3.16
Estimated blood loss (ml)	264 ± 46	261 ± 47
Crystalloid infused during surgery (ml)	928 ± 61	1018 ± 56
Admission to surgery interval (days)	1.92 ± 0.27	2.12 ± 0.37

TABLE II. *Systolic arterial pressure (mm Hg) (mean ± SEM) before operation and minimum values during operation*

	GA group	SAB group
Before operation	147 ± 6	146 ± 6
Minimum systolic pressure during operation	102 ± 5	82 ± 4

After surgery, Pa_{O_2} was decreased significantly in GA group (tables III and IV). There was, however, no change in mean Pa_{O_2} in SAB group either during or after surgery. All blood-gas measurements in SAB group were made with the patient breathing room air. Pa_{O_2} values in GA group during operation are not quoted as these patients received FI_{O_2} 0.33. Regression analysis applied to the preoperative blood-gas data failed to reveal a significant correlation between age and Pa_{O_2}.

Pa_{CO_2} values were small in both groups (mean 4.35 kPa), but in GA group, mean Pa_{CO_2} and base deficit were significantly greater during operation. The decrease in pH and increase in base deficit in both groups, whilst statistically significant (table IV), were not clinically noteworthy.

Table V shows the cumulative mortality rates in each group over a 4-week period after surgery. Fewer died in SAB group, but the difference was not statistically significant (χ^2 test with Yates' correction). The overall mortality was 13%.

One death in the 4th week in SAB group was unrelated to surgery, being a result of acute cholecystitis and ascending cholangitis, with septicaemia. Other causes of death in SAB group included congestive cardiac failure and pneumonia (1), pulmonary thromboembolism (1), bronchopneumonia (1), and a combination of carcinomatosis and cardiac failure (1).

TABLE III. *Arterial blood-gas measurements ($F_{I_{O_2}}$ = 0.209) before induction, 60 min after induction and 60 min after end of anaesthesia (mean values ± SEM). Pa_{O_2} values in GA during operation omitted (see text). Significant differences between arrowed groups by unpaired Student's t test:* *$P = <0.05$; **$P = <0.001$; ***$P = <0.01$

		GA group		SAB group
Pa_{O_2} (kPa)	Pre-op.	9.15±0.16		8.94±0.10
	60 min intra-op.	—		8.91±0.24
	60 min post-op.	8.52±0.19	←*→	9.19±0.25
Pa_{CO_2}(kPa)	Pre-op.	4.34±0.08		4.36±0.10
	60 min intra-op.	5.16±0.15	←**→	4.36±0.09
	60 min post-op.	4.39±0.09		4.38±0.09
pH (units)	Pre-op.	7.462±0.005		7.46±0.008
	60 min intra-op.	7.367±0.01		7.438±0.007
	60 min post-op.	7.425±0.005		7.439±0.006
Base excess (mmol litre^{-1})	Pre-op.	−0.03±0.32		−0.18±0.46
	60 min intra-op.	−3.1±0.36	←***→	−1.65±0.39
	60 min post-op.	−2.44±0.31		−1.62±0.4

TABLE IV. *Changes (mean ± SEM) in blood-gas measurements (value before operation minus value after operation) in each group.* *$P < 0.001$ *(paired Student's t test)*

	GA group	SAB group
Pa_{O_2} (kPa)	+0.675±0.16*	−0.124±0.17
Pa_{CO_2} (kPa)	−0.031±0.05	−0.019±0.07
pH (units)	+0.037±0.005*	+0.029±0.005*
Base excess (mmol litre^{-1})	+2.274±0.24*	+1.548±0.24*
Axillary temperature (°C)	+0.606±0.156*	+0.635±0.12*

TABLE V. *Mortality rate in both groups of patients at differing periods after surgery. Cumulative totals in each group. Overall 4-week mortality rate* 13%

	Days after operation			
	0–7	8–14	15–21	22–28
GA group ($n = 51$)	4 (7.8%)	6 (11.8%)	8 (15.7%)	8 (15.7%)
SAB group ($n = 49$)	2 (4.1%)	2 (4.1%)	4 (8.2%)	5 (10.2%)

Causes of death in GA group included bronchopneumonia (3) (one with pulmonary thromboembolism); two other patients died of pulmonary thromboembolism, one of myocardial infarction and one from complications of heart block; in one patient the cause of death was not determined.

DISCUSSION

The patients receiving spinal anaesthesia showed no change in arterial P_{O_2} or P_{CO_2} during and after operation. This is in agreement with the findings of de Jong (1965), that the development of a spinal block had no effect on Pa_{O_2} and Pa_{CO_2} in patients undergoing various procedures. Respiratory function measurement has shown no deterioration under spinal anaesthesia in obese patients (Catenacci and Sampathachar, 1969) or those with chronic obstructive pulmonary disease (Paskin, Rodman and Smith, 1969). However, patients in GA group showed a significant decrease in Pa_{O_2} of about 0.68 kPa. Wishart, Williams and Smith (1977) found a decrease of a similar extent in patients receiving three different general anaesthetic techniques for fractured neck of femur (halothane in oxygen in a closed circuit; halothane, nitrous oxide and oxygen via a Magill circuit, and artificial ventilation with 66% nitrous oxide in oxygen with pancuronium for neuromuscular blockade). Since the completion of this study it has been noticed that serial measurements of P_{O_2} in arterial blood samples from patients undergoing general anaesthesia with halothane have caused the calibration of the Radiometer ABL1 oxygen electrode to drift upwards. This has resulted in approximately a 10% overestimation of Pa_{O_2} after 1 h. This error occurred only after samples containing halothane had been analysed. This finding has been noted before (Severinghaus et al., 1971) and the findings from this hospital have been published

(Douglas et al., 1978). Under normal conditions, the Radiometer ABL 1 has been shown to be as accurate as conventional blood-gas apparatus (Selman and Tait, 1976). Thus, the present study may have underestimated the decrease in Pa_{O_2} after halothane anaesthesia, perhaps of the order of 1.5 kPa at 1 h after the end of anaesthesia (Douglas et al., 1978). This would accentuate further the difference in oxygenation after operation between the two groups.

Patients in this study had overall mean Pa_{O_2} 9.04 kPa and Pa_{CO_2} 4.35 kPa before operation. These values are similar to those in comparable patients studied by Wishart, Williams and Smith (1977), Phillips and Tomlin (1977) and McLaren, Stockwell and Reid (1978). Martin (1977) found a smaller mean Pa_{O_2} before operation in a similar group of patients. The question arises as to whether Pa_{O_2} values are smaller than one might expect in this age group. Mean Pa_{O_2} of 50 uninjured supine elderly patients (ages 60–91, mean 73 yr) was found by Ward and colleagues (1966) to be 10.24 kPa and mean Pa_{CO_2} was 4.52 kPa. If it is permissible to extrapolate published regression lines for age against Pa_{O_2} beyond the age of 60 yr (Raine and Bishop, 1963; Conway, Payne and Tomlin, 1965; Marshall and Millar, 1965; Gillies et al., 1977) then the preoperative Pa_{O_2} values in the present study would seem smaller than expected. However, extrapolation of regression lines is statistically unacceptable and that this would be misleading is supported by the poor correlation between age and Pa_{O_2} in the present study and that of Martin (1977). The fact that Pa_{O_2} values return to values greater than those before operation once the patient has recovered and is mobilized (I. Gray, unpublished data) lends support to the hypothesis that the value of Pa_{O_2} before operation is reduced. The aetiology of this relative hypoxaemia cannot be determined in the present study. Clinically unsuspected hypoxaemia is seen commonly after fractures (Tachakra and Sevitt, 1975) and it has been postulated that this is a result of fat embolus (Ross, 1970). Prolonged recumbency (10 days in bed) may cause an increase in the alveolar–arterial oxygen partial pressure differences in healthy young males (Cardus, 1967). Both subclinical fat embolism and recumbency may be implicated in the present study.

There was a lower mortality in SAB group, although this was not statistically significant. McLaren, Stockwell and Reid (1978) studying a similar group of 55 patients with fractured neck of femur compared general anaesthesia (nitrous oxide, opiate, relaxant, IPPV technique) with unilateral spinal anaesthesia and sedation with Entonox and a continuous infusion of Althesin. They found a significantly smaller mortality in the spinal anaesthesia group. In GA group, nine patients died within 4 weeks—a mortality rate of 31%. One patient (3.8%) died in SAB group. Speculation on any improved mortality resulting from spinal anaesthesia would include a possible reduction in the frequency of pulmonary thromboembolism and prevention of further reduction in respiratory function after surgery. The overall mortality within 4 weeks of surgery in the present study was 13% which compares with mortality rates of 10.4% (Barnes et al., 1976) and 20% (Gallannaugh, Martin and Millard, 1976) in other large series.

Our patients were unselected before allocation to spinal or general anaesthesia. It is the policy in the authors' hospital to operate on all patients with fractured neck of femur on the first day after admission, unless they would not obviously benefit from the procedure or have gross cardiac failure or uncontrolled diabetes mellitus. Many of the patients in this study were operated upon on Monday morning, no surgery on fractured necks of femur being performed over the weekend. This accounts for the mean delay of 2 days between admission and surgery.

The need for sedation in the spinal anaesthesia group was small as the block was bilateral and of sufficient height to abolish the discomfort of lying on the orthopaedic operating table. Smaller quantities of analgesic drugs were required in SAB group after surgery as the spinal block persisted into the period after operation.

The safety and lack of sequelae of spinal anaesthesia have been established in large series (Dripps and Vandam, 1954; Noble and Murray, 1971). Our study shows that the technique is at least as safe as general anaesthesia for the elderly patient with fractured neck of femur, and indeed may be beneficial. The subjective opinion of the orthopaedic ward staff certainly favoured the use of spinal anaesthesia as these patients were easier to nurse and were much less confused—a major problem with many patients in the general anaesthetic group. Despite the occasional technical difficulty and time taken to perform the block, spinal anaesthesia appears to be suitable and perhaps the preferred method for lower limb surgery in the elderly, injured patient.

REFERENCES

Aldrete, J. A., Davis, H. S., and Hingson, R. A. (1967). Anaesthesia factors in the surgical management of hip fractures. *J. Trauma*, **7**, 818.

Allen, H. L., and Metcalf, D. W. (1965). Fractured hip: a study of anesthesia in the aged. *Anesth. Analg. (Cleve.)*, **44**, 408.

Barnes, R., Brown, J. T., Garden, R. S., and Nicholl, E. A. (1976). Subcapital fractures of the femur. A prospective review. *J. Bone Joint Surg.*, **58**, 2.

Cardus, D. (1967). O_2 alveolar–arterial tension difference after 10 days recumbency in man. *J. Appl. Physiol.*, **23**, 934.

Catenacci, A. J., and Sampathachar, K. R. (1969). Ventilatory studies in the obese patient during spinal anesthesia. *Anesth. Analg. (Cleve.)*, **48**, 48.

Conway, C. M., Payne, J. P., and Tomlin, P. J. (1965). Arterial oxygen tensions of patients awaiting surgery. *Br. J. Anaesth.*, **37**, 405.

Douglas, I. H. S., McKenzie, P. J., Ledingham, I. McA., and Smith, G. (1978). Effect of halothane on P_{O_2} electrode. *Lancet*, **2**, 1370.

Dripps, R. D., and Vandam, L. D. (1954). Long-term follow up of patients who received 10 098 spinal anesthetics. *J.A.M.A.*, **156**, 1486.

Gallannaugh, S. C., Martin, A., and Millard, P. (1976). Regional survey of femoral neck fractures. *Br. Med. J.*, **2**, 1496.

Gillies, I. D. S., Petrie, A., Morgan, M., and Sykes, M. K. (1977). Analysis of possible factors influencing P_{aO_2} and ($P_{AO_2}-P_{aO_2}$) in patients awaiting operation. *Br. J. Anaesth.*, **49**, 427.

Honkonen, K., Tarkkanen, L., and Julkunen, H. (1971). Femoral neck fracture during and after surgery. *Acta Med. Scand.*, **189**, 173.

de Jong, R. H. (1965). Arterial carbon dioxide and oxygen tensions during spinal block. *J.A.M.A.*, **191**, 698.

McLaren, A. D., Stockwell, M. C., and Reid, V. T. (1978). Anaesthetic techniques for surgical correction of fractured neck of femur. A comparative study of spinal and general anaesthesia in the elderly. *Anaesthesia*, **33**, 10.

Marshall, B. E., and Millar, R. A. (1956). Some factors influencing postoperative hypoxaemia. *Anaesthesia*, **20**, 408.

Martin, V. C. (1977). Hypoxaemia in elderly patients suffering from fractured neck of femur. *Anaesthesia*, **32**, 852.

Modig, J., Busch, C., Olerud, S., Saldeen, T., and Waernbaum, G. (1975). Arterial hypotension and hypoxaemia during total hip replacement: the importance of thromboplastic products, fat embolism and acrylic monomers. *Acta Anaesthesiol. Scand.*, **19**, 28.

Noble, A. B., and Murray, J. G. (1971). A review of the complications of spinal anaesthesia with experiences in Canadian teaching hospitals from 1959 to 1969. *Can. Anaesth. Soc. J.*, **18**, 5.

Paskin, S., Rodman, T., and Smith, T. C. (1969). Effect of spinal anaesthesia on the pulmonary function of patients with chronic obstructive pulmonary disease. *Ann. Surg.*, **169**, 35.

Phillips, G., and Tomlin, P. J. (1977). Arterial oxygen tensions in elderly and in injured elderly patients. *Br. J. Anaesth.*, **49**, 514.

Raine, J. M., and Bishop, J. M. (1963). A–a difference in O_2 tension and physiological deadspace in normal man. *J. Appl. Physiol.*, **18**, 284.

Ross, A. P. J. (1970). The fat embolism syndrome: with special reference to the importance of hypoxia in the syndrome. *Ann. R. Coll. Surg.*, **46**, 159.

Scott, D. B., and Thorburn, J. T. (1975). Spinal anaesthesia. *Br. J. Anaesth.*, **47**, 421.

Selman, B. J., and Tait, A. R. (1976). Towards blood-gas autoanalysis: an evaluation of the Radiometer ABL I. *Br. J. Anaesth.*, **48**, 487.

Severinghaus, J. W., Weiskopf, R. B., Nishimura, M., and Bradley, A. F. (1971). Oxygen electrode errors due to polarographic reduction of halothane. *J. Appl. Physiol.*, **31**, 640.

Tachakra, S. S., and Sevitt, S. (1975). Hypoxaemia after fractures. *J. Bone Joint Surg.*, **57**, 197.

Ward, R. J., Tolas, A. G., Benveniste, R. J., Hansen, J. M., and Bonica, J. J. (1966). Effect of posture on normal arterial blood-gas tensions in the aged. *Geriatrics*, **21**, 139.

Wishart, H. Y., Williams, T. I. R., and Smith, G. (1977). A comparison of the effect of three anaesthetic techniques on postoperative arterial oxygenation in the elderly. *Br. J. Anaesth.*, **49**, 1259.

COMPARAISON DES EFFETS DE L'ANESTHESIE RACHIDIENNE ET DE L'ANESTHESIE GENERALE SUR L'OXYGENATION POSTOPERATOIRE ET LA MORTALITE PERIOPERATOIRE

RESUME

Cent malades se présentant pour traitement chirurgical d'une fracture du col du fémur ont été répartis afin de recevoir soit une anesthésie rachidienne (SAB), soit une anesthésie générale (GA). Avant l'opération, la P_{aO_2} moyenne était de 9,04 kPa. On a constaté une importante diminution de la P_{aO_2}: 0,68 kPa dans le groupe GA 1 h après l'intervention chirurgicale, alors que les valeurs sang-gaz demeuraient sans changement dans le groupe SAB. Huit malades (15,7%) du groupe GA et cinq malades 10,2%) du groupe SAB sont décédés dans les quatre semaines qui ont suivi l'opération. La différence n'est pas significative du point de vue statistique.

VERGLEICH DER EFFEKTE VON SPINALER UND ALLGEMEINER ANÄSTHESIE AUF POSTOPERATIVE SAUERSTOFFAUFNAHME UND PERIOPERATIVE STERBLICHKEIT

ZUSAMMENFASSUNG

Ein hundert Patienten mit Oberschenkelhalsbruch erhielten vor der Operation entweder spinale (SAB) oder allgemeine Anästhesie (GA). Vor der Operation betrug der mittlere P_{aO_2} 9,04 kPa. Bei der GA-Gruppe gab es 1 Stunde nach der Operation eine deutliche Senkung von P_{aO_2} auf 0,68 kPa, während in der SAB-Gruppe die Blutgaswerte

unverändert blieben. Acht Patienten (15,7%) der GA-Gruppe und fünf Patienten (10,2%) der SAB-Gruppe starben innerhalb von 4 Wochen nach der Operation. Der Unterschied ist statistisch nicht von Bedeutung.

COMPARACION DE LOS EFECTOS DE LA ANESTESIA ESPINAL Y DE LA ANESTESIA GENERAL EN OXIGENACION POSTOPERATORIA Y MORTALIDAD PERIOPERATORIA

SUMARIO

Se seleccionó a 100 pacientes que estaban por someterse a una operación quirúrgica del cuello del fémur para administrarles anestesia ya sea espinal (SAB) ya sea general (GA). Antes de la operación el Pa_{O_2} era de 9,04 kPa. Hubo un descenso significativo del Pa_{O_2} de 0,68 kPa en el grupo GA 1 hora después de la operación, mientras los valores gas-sangre del grupo SAB permanecieron sin cambio. Ocho pacientes (15.7%) del grupo GA y cinco pacientes (10.2%) del grupo SAB fallecieron dentro de 4 semanas desde la operación. No fue significativa la diferencia desde el punto de vista estadístico.

Br. J. Anaesth. (1980), **52**, 55

LUMBAR EXTRADURAL INJECTION PRESSURES IN PREGNANT WOMEN

An investigation of relationships between rate of injection, injection pressures and extent of analgesia

R. P. HUSEMEYER AND D. C. WHITE

SUMMARY

Before the induction of labour in 34 pregnant women 1.5% lignocaine 10 ml was injected into the lumbar extradural space at constant rates between 0.143 and 0.333 ml s^{-1}. Injection pressures and residual pressures were recorded and the extent of analgesia to pinprick was assessed. No significant correlation was found between the rate of injection and injection pressures or residual pressures over the range investigated. Analgesia was significantly more extensive on the side dependent during injections, but there was no significant correlation between the overall extent of analgesia and the rate of injection, injection pressures or residual pressures in the extradural space. It is concluded that there is no advantage from rapid extradural injections.

The pressure in the extradural space has been the subject of numerous investigations since Janzen (1926) demonstrated a subatmospheric pressure on piercing the ligamentum flavum in the course of a lumbar puncture. One aspect which has received little attention is the instantaneous change in pressure at the site of injection and its relationship to the speed of injection and extent of analgesia. It is assumed generally that the pressure generated at the site of injection is related directly to the rate of injection, but we have found no reliable data to support this assumption. Usubiaga, Wikinski and Usubiaga (1967) reported inaccuracies from artefacts in a study which aimed to measure extradural pressure during injections of local anaesthetics and to compare extradural pressure/volume curves with the extent of anaesthetic blockade. Resorting to measurement of residual pressure 2 min after extradural injection of 2% lignocaine 10 ml over 15 s at the second lumbar intervertebral level, the same authors reported that, in general, a higher level of anaesthesia was associated with greater residual pressures.

The present study was carried out to investigate the relationships between the rate of injection, injection pressures and the extent of analgesia in pregnant women.

PATIENTS AND METHODS

The study was conducted on 34 women who had requested extradural analgesia for labour induced at or near term. All the patients were of normal body build and ranged in age from 17 to 36 yr (mean 28.2 yr). Pressure curves were recorded and extradural analgesia was established before the induction of labour to exclude any influence of the uterine contractions on the pressure in the extradural space (Galbert and Marx, 1974).

With the patients in the flexed left-lateral decubitus position, the injection site was prepared and a 17-gauge Tuohy needle was inserted into the extradural space between the 2nd and 3rd lumbar vertebrae with the bevel directed cephalad. Entry of the needle point into the space was confirmed by loss of resistance to injection of not more than 1 ml of air.

The injection and recording system (fig. 1) consisted of a 10-ml syringe and 100-cm length of nylon manometer tube, pre-filled with 1.5% lignocaine solution, connected by means of a three-way tap to an electromanometer (Elema-Schönander transducer) and pen recorder, calibrated in cm H_2O. Before connecting the manometer tube to the hub of the Tuohy needle, extradural pressure was allowed to equilibrate with the atmosphere across the needle. Therefore all injections began with the same zero reference point (atmospheric pressure) in the extradural space at the site of injection.

R. P. HUSEMEYER, M.R.C.O.G., Division of Perinatal Medicine; D. C. WHITE, F.F.A.R.C.S., Division of Anaesthesia; Clinical Research Centre and Northwick Park Hospital, Watford Road, Harrow, Middlesex, HA1 3UJ.

0007-0912/80/010055-06 $01.00

© Macmillan Journals Ltd 1980

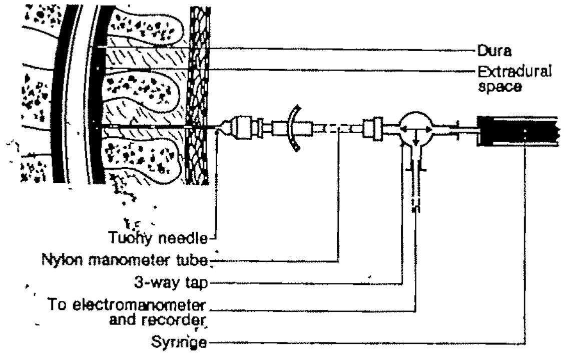


FIG. 1. Diagram of injection and recording system.

Injections of 1.5% lignocaine 10 ml were delivered at a constant rate over a time range of 30–70 s (0.333–$0.143\ \text{ml}\cdot\text{s}^{-1}$) using a compressed carbon dioxide-powered hydraulic syringe pump (fig. 2). Pressure curves were recorded during each extradural injection and the residual pressure was recorded for 3–5 min thereafter (fig. 3).

Each pressure curve (P_1) recorded in this way included a component of pressure resulting from the resistance to flow through the injection system. In order to measure the component of pressure attributable to the resistance of the system, injections were repeated to the atmosphere at the same rate, through the same system, with the Tuohy needle point at the same level. Pressure curves (P_2) representing the resistance of the system were recorded in each instance. The instantaneous extradural space pressure at the site of injection was determined by superimposing the curves (P_1 and P_2) and is given by $P_1 - P_2$ (fig. 3).

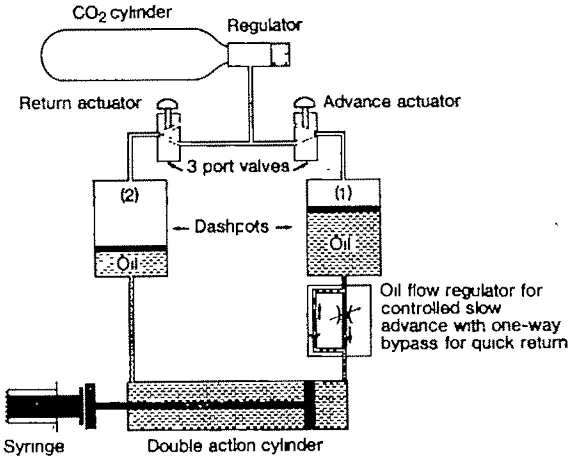


FIG. 2. Diagram of syringe pump. "Advance actuator" depressed: Carbon dioxide pressurizes dashpot (1) driving oil via flow regulator to advance plunger. Gas from dashpot (2) exits via open port of Return 3-port valve. "Return actuator" depressed: Carbon dioxide pressurizes dashpot (2) returning plunger with oil passing unrestricted via one-way bypass valve. Gas from dashpot (1) exits via open port of Advance 3-port valve.

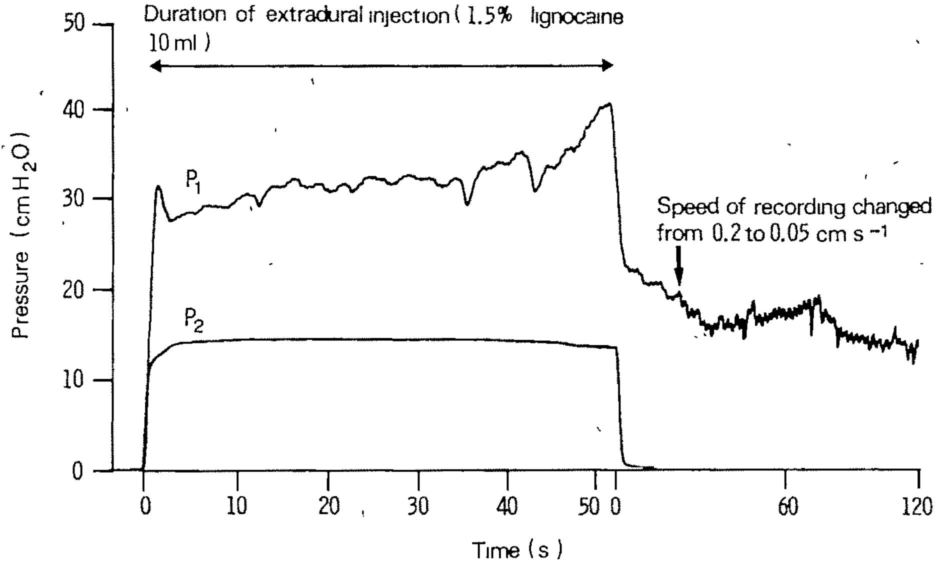


FIG. 3. Typical pressure record during injection into extradural space (P_1) and to atmosphere (P_2).

TABLE I. *Mean (±SD) and range of extradural injection pressures and residual pressures*

	Injection pressures (cm H_2O)			Residual pressures (cm H_2O)	
	Initial	Terminal	Maximum	After 1 min	After 2 min
Mean (±SD)	23.2 (±14.2)	28.1 (±13.5)	29.0 (±14.0)	13.0 (±4.4)	11.4 (±3.7)
Range	6.0–62.0	10.5–73.0	10.5–73.0	3.5–23.5	2.0–18.0

Following the injection of 1.5% lignocaine 10 ml as described, a catheter was passed to 3 cm beyond the point of the Tuohy needle and the needle was removed. Ten minutes after the injection the patients were turned supine and after a further 10 min the distribution of analgesia to pinprick, according to the dermatome maps of Keegan and Garrett (1948) was recorded on each side. The extent of analgesia was expressed as the total number of spinal segments blocked, that is the sum of the number of analgesic segments on the left and right sides.

The regression lines in figures 4–8 were calculated by the method of least squares. The *t* test for paired data was used to compare the extent of analgesia on dependent and non-dependent sides.

RESULTS

From the recordings obtained the initial, terminal and maximum injection pressures and the residual pressures 1 min and 2 min after injection were calculated (table I).

Although a wide range of injection pressures was observed, the pattern of pressure curves was similar. Fluctuations synchronous with respiratory movements and maternal arterial pulse were seen frequently (fig. 3).

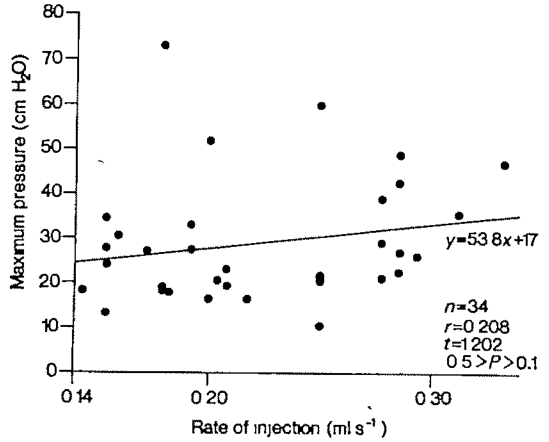


FIG. 4. Relation between rate of extradural injection and maximum extradural injection pressure.

Maximum injection pressures corresponded with the terminal injection pressures in 24 subjects. In five subjects maximum injection pressure corresponded with the initial injection pressure and in the remaining

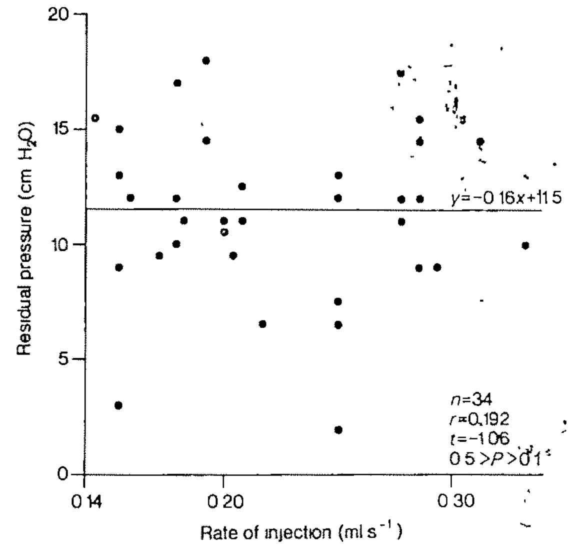


FIG. 5. Relation between rate of extradural injection and residual extradural pressure (2 min after injection).

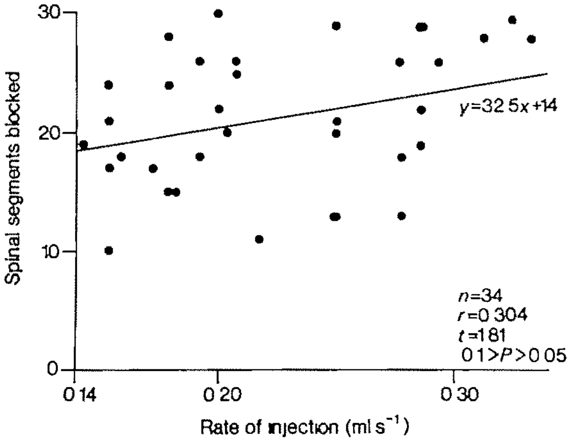


FIG. 6. Relation between rate of extradural injection and extent of analgesia.

five subjects the maximum pressure was up to 2.5 cm H_2O greater than the initial or terminal injection pressure.

Over the range investigated there was no significant correlation between the rate of injection and the maximum injection pressure (fig. 4), nor was there a significant correlation between the rate of injection and the residual pressure 1 min or 2 min after injection (fig. 5).

The extent of analgesia showed no significant correlation with the rate of injection (fig. 6), maximum injection pressure (fig. 7) or residual pressure 2 min after injection (fig. 8).

The number of analgesic segments on the side dependent during and 10 min after injection (mean ± SD = 12.1 ± 2.7) was significantly greater ($P < 0.001$) than the number of analgesic segments on the non-dependent side (mean ± SD = 9.1 ± 4.0). In one patient analgesia was confined entirely to the dependent side. The injection pressure curve in this patient with unilateral block showed no recognizable features which were different from the pressure curves of other patients and subsequently a "top-up" dose of 0.375% bupivacaine 8 ml (with the unblocked side dependent) produced symmetrical analgesia.

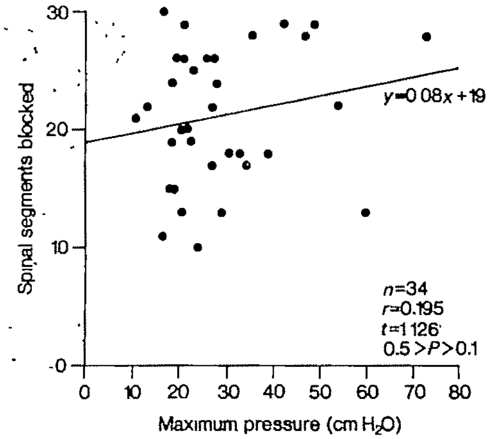


FIG. 7. Relation between maximum extradural injection pressure and extent of analgesia.

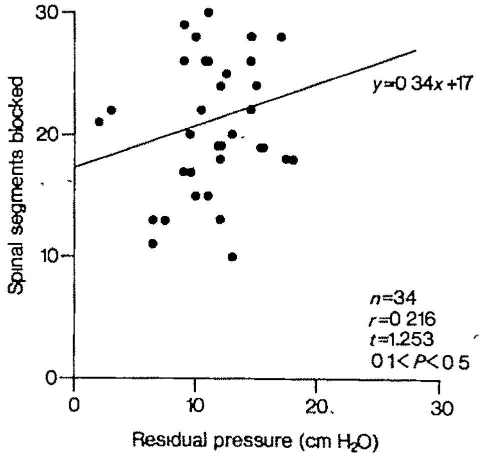


FIG. 8. Relation between residual extradural pressure (2 min after injection) and extent of analgesia.

DISCUSSION

The maximum pressures generated at the site of injection showed wide variation unrelated to the speed of injection over the range investigated. We assume two explanations for this. First, the compliance of the extradural space depends on the composition and resistance of its tissues, which may vary between individuals. Second, and probably more important, is that the extradural space is not confined, but communicates with the paravertebral space via the intervertebral foramina. Injection pressures may therefore depend as much on the rate of leakage as on the rate of injection.

Reports of untoward effects on patients suggest that very rapid extradural injections may generate pressures greater than those which we have observed. Erdemir, Soper and Sweet (1965) found that at the rate of 1 ml s^{-1} a considerable proportion of the subjects complained, in many cases bitterly, of discomfort during injection. Usubiaga and colleagues (1967) reported that "dizziness, nausea, frontal oppression, contracture of the back muscles and tachypnoea were observed during rapid injections." No untoward effects occurred in the subjects in our study and although the maximum rate of injection (0.333 ml s^{-1}) was slower than the rates which have been used by others, approximately half the injections were delivered more rapidly than can be achieved without extreme effort through a standard extradural catheter (Portex reference number 100/380/300).

There have been many reports concerning factors which influence the extent of extradural analgesia and the conclusions of some authors have been at variance with others, for example, Bromage (1962, 1969) and Grundy and co-workers (1978). In this study we ignored other factors in examining the relationships between the rate of injection, injection pressure and the extent of analgesia as all the subjects were pregnant women of normal build and similar age and all received 1.5% lignocaine 10 ml at the same lumbar vertebral level in the left lateral position.

Resistance to spread of solutions within the space and the rate of leakage from the space may vary independently and may explain our failure to demonstrate a significant correlation between either the rate of injection or the injection pressure and the extent of analgesia. Erdemir, Soper and Sweet (1965) investigated two rates of injection (1 ml s^{-1} and 0.333 ml s^{-1}) given randomly at the same lumbar interspace 1 week apart in 18 healthy male volunteers and found that the upper level of analgesia was on average 0.7 dermatome higher with the faster injections. It is relevant, however, that sacral analgesia was incomplete in five subjects after fast injections compared with only two after slow injections, which suggests that the different extent of analgesia in the two groups may have been even less if it had been assessed in terms of the total number of analgesic segments rather than merely the upper level of analgesia.

The effect of lateral position resulted in a greater extent of analgesia on the dependent side, which was both statistically and clinically significant, and is in agreement with the finding of Grundy, Rao and Winnie (1978), of an average difference of two segments between dependent and non-dependent sides in patients kept in the lateral position for at least 15 min. This effect appears to be clinically useful, whereas we can demonstrate no advantage from rapid extradural injections.

ACKNOWLEDGEMENTS

We thank Mr Adam Platt, Division of Bioengineering, Clinical Research Centre, for assistance with the design and construction of the syringe pump used in this study.

REFERENCES

Bromage, P. R. (1962). Spread of analgesic solutions in the epidural space and their site of action: a statistical study. *Br. J. Anaesth.*, **34**, 161.

—— (1969). Ageing and epidural dose requirements. *Br. J. Anaesth.*, **41**, 1016.

Erdemir, H. A., Soper, L. E., and Sweet, R. B. (1965). Studies of factors affecting peridural anesthesia. *Anesth. Analg.* (*Cleve.*), **44**, 400.

Galbert, M. W., and Marx, G. F. (1974). Extradural pressure in the parturient patient. *Anesthesiology*, **40**, 499.

Grundy, E. M., Ramamurthy, S., Patel, K. P., Mani, M., and Winnie, A. P. (1978). Extradural analgesia revisited: a statistical study. *Br. J. Anaesth.*, **50**, 805.

—— Rao, L. N., and Winnie, A. P (1978). Epidural anesthesia and the lateral position. *Anesth. Analg.* (*Cleve.*), **57**, 95.

Janzen, E. (1926). Der negative Vorschlag bei lumbal Punktion. *Dtsch. Z. Nervenheilkd*, **94**, 280.

Keegan, J. J., and Garrett, F. D. (1948). The segmental distribution of the cutaneous nerves in the limbs of man. *Anat. Rec.*, **102**, 409.

Usubiaga, J. E., Usubiaga, L. E., Brea, L. M., and Goyena, R. (1967). Epidural and subarachnoid space pressures and relation to post-spinal anesthesia headache. *Anesth. Analg.* (*Cleve.*), **46**, 293.

—— Wikinski, J. A., and Usubiaga, L. E. (1967). Epidural pressure and its relation to spread of anesthetic solutions in epidural space. *Anesth. Analg.* (*Cleve.*), **46**, 440.

PRESSION POUR LES INJECTIONS LOMBAIRES EXTRADURALES CHEZ LES FEMMES ENCEINTES

Recherche des relations qui existent entre le taux d'injection, les pressions d'injection et l'importance de l'analgesie

RESUME

Avant l'induction du travail, on a injecté 10 ml de lignocaine à 1,5% dans l'espace lombaire extradural de 34 femmes enceintes, à des taux constants se situant entre 0,143 et 0,333 ml s^{-1}. On a enregistré les pressions d'injection et les pressions résiduelles, et estimé l'importance de l'analgésie aux piqûres d'aiguilles. On n'a trouvé aucune corrélation significative entre le taux d'injection et les pressions d'injection ou les pressions résiduelles sur l'ensemble de la plage faisant l'objet ces recherches. L'analgésie a été beaucoup plus significative sur le côté dépendant pendant les injections, mais il n'y a eu aucune corrélation significative entre l'importance totale de l'anesthésie et le taux d'injection, les pressions d'injection ou les pressions résiduelles dans l'espace extradural. On en a conclu qu'il n'y avait aucun avantage à faire des injections extradurales rapides.

LUMBALER EXTRADURALER INJECTIONSDRUCK BEI SCHWANGEREN FRAUEN

Eine Untersuchung der Beziehungen zwischen Injektionshäufigkeit, Injektionsdrucken und Ausmass der Analgie

ZUSAMMENFASSUNG

Vor Weheneinleitung wurden 34 Frauen 1,5%iges 10 ml Lignocain in den lumbalen Extraduralraum injeziert—in konstanten Mengen zwischen 0,143 und 0,333 ml s^{-1}. Injektions- und Residualdrucke wurden aufgezeichnet, und das Ausmass der Analgie auf Nadelstich untersucht. Keine wesentlichen Korrelationen wurden zwischen Injektionsrate, Injektions- und Residualdrucken festgestellt. Analgie war deutlich umfassender auf der entsprechenden Seite während der Injektionen, doch gab es keine wesentlichen Korrelationen im extraduralen Raum zwischen Injektionsrate, Injektions- und Residualdrucken einerseits und dem Gesamtausmass der Analgie andererseits. Daraus wird geschlossen, dass schnelle extradurale Injektionen keinen Vorteil bedeuten.

PRESIONES DEBIDAS A INYECCION EXTRADURAL LUMBAR EN MUJERES EMBARAZADAS

Investigación de la relación entre el ritmo de inyección, las presiones de inyección y el alcance de la analgesia

SUMARIO

Se inyectó 10 ml de lignocaina a 1.5% en el espacio extradural lumbar de 34 mujeres embarazadas antes de la inducción del parto en ritmos constantes entre 0,143 y 0,333 ml s^{-1}. Se registraron las presiones de la inyección y las presiones residuales y se evaluó el alcance de la analgesia con la punta de un alfiler. No se halló correlación significativa alguna entre el ritmo de inyección y las presiones de inyección o las presiones residuales en la serie investigada. La analgesia fue mucho más extensa del lado donde se hacían las inyecciones, pero no hubo una correlación significativa entre el alcance global de la analgesia y el ritmo de inyección, las presiones de inyección o las presiones residuales en el espacio extradural. Se concluye que no existe ninguna ventaja en una rápida inyección extradural.

Br. J. Anaesth. (1980), **52**, 61

THE ANAESTHETIC MACHINE—A STUDY OF FUNCTION AND DESIGN

G. BOQUET, J. A. BUSHMAN AND H. T. DAVENPORT

SUMMARY

A study of the time and motion of the anaesthetists' routine activities was made using conventional equipment. Films of manual and visual movements were studied in detail and the expectations of certain consultant anaesthetists regarding apparatus were recorded. Models of apparatus were used to test their acceptability. A modular system appeared preferable to a work station or to adaptation of present designs. More work and the construction of prototypes are indicated if the anaesthetic machine is to be modernized.

The aim of this study was to design an anaesthetic machine and some associated equipment with emphasis on the anaesthetist's working procedures and ergonomic factors concerning control and display. The designer (G. B.) had never previously been associated with the anaesthetic procedure, hence he had no preconceived ideas. Broad, preconceived ideas were contributed by the anaesthetist preceptors (J. A. B. and H. T. D.). For example, it was considered that a ventilator and monitoring devices were to be integral parts of a modern anaesthetic machine. The study tried initially to produce an understanding of how the anaesthetist used individual pieces of equipment and how he related to the surrounding activities.

An analysis of the anaesthetist's work was carried out during the induction and maintenance of anaesthesia. For each activity we attempted to define: duration, frequency, relative importance, and relationship to other activities and equipment.

METHODS

To study the anaesthetic procedure 15 operations were analysed using a filming technique. Initially, a single video film was made of an anaesthetic in progress, but on studying this there were too many limitations when using a single camera. The anaesthetist's activities were carried out over a wide area and it was impossible to record them all with a single conventional camera. It was found that there was a distinct difference between his visual and his manual activities and it was felt necessary to study both functions separately. Manual activities were recorded by a single video unit positioned behind the anaesthetist's working area where, with a wide-angled lens, all the equipment the anaesthetist would be likely to use could be included. Visual movements were more difficult to record, but this was achieved finally by using a Nac eye mark recorder. This device consists of a head piece which the subject wears throughout the recording time and, via a system of lenses and half mirrors, an image is produced that can be recorded on the video tape. The image is a view in the direction in which the subject is looking and on that image, by means of a light reflected off the cornea of his eye, a small arrow shows precisely on what object his eye is focusing. The angle of the full image in the horizontal and vertical plane is only 80° and therefore occasionally when the wearer looked at an object outside this viewing angle the arrow disappeared. However, over the duration of filming we undertook the number of times this happened was negligible.

Filming was carried out at two London Hospitals, St Peter's, Covent Garden, and Northwick Park, Harrow. The two hospitals have different operating theatre environments: Northwick Park is modern and newly equipped, whilst St Peter's is older and less sophisticated.

The four anaesthetists studied were one very experienced consultant, two experienced registrars and one relatively inexperienced senior house officer. Sixteen hours of filming was carried out and included a representative cross-section of the types of general anaesthetics performed at these hospitals.

Once the filming was concluded an extensive study was made of 31 manual and 26 visual activities,

---

GAVIN BOQUET, Industrial Designer, 2 Princes Square, London W2. JOHN A. BUSHMAN, L.M.S.S.A., F.F.A.R.C.S., COMPANION I.E.E., F.INST. M.C., Research Department of Anaesthetics, Royal College of Surgeons, London WC2A 3PN. HAROLD T. DAVENPORT, M.B.,CH.B., F.R.C.P.(C), F.F.A.R.C.S., Department of Anaesthetics, Northwick Park Hospital, Harrow, Middlesex.

0007-0912/80/010061-07 $01.00

© Macmillan Journals Ltd 1980

these being noted every 0.5 s. These data were then entered onto a computer file to facilitate sorting and statistical analysis. The processed data were collated as follows:

(1) The amount of time during which each activity occurred was expressed as a portion of the total anaesthetic time.
(2) The percentage of time each manual activity occurred with each visual activity.
(3) At what time and for how long each individual activity occurred.
(4) The frequency with which each individual activity occurred before or after another.
(5) How often a particular sequence of activities occurred.

To complement this numerical information it was thought necessary to produce an importance rating for each manual and visual activity. Seven consultant anaesthetists were asked to list manual activities and the visual activities in order of importance to the patient's well being. An average importance rating, ranging from 0 to 10, was produced for each activity.

RESULTS

(1) *The percentage of time each activity occurred* (fig. 1)

It was apparent that the patient or surgical field took up approximately 60% of the anaesthetist's visual activity time, 40% of his visual activity time being occupied elsewhere. Of the other activities, the anaesthetic reservoir bag was the most observed dynamic display, taking up 10% of time. Other static and dynamic displays, that is, monitors, flow meters and vaporizers; each took up 3% of visual time and were observed less than the charts or sphygmomanometer. Visual contact with the ventilator was small, about 1%. However, the fact that the bellow's movement can be heard in the type used may explain why the anaesthetist did not look at the ventilator except when altering controls. Over the periods of recording the emergency oxygen switch was not used.

With regard to manual activity, during 72% of their time the anaesthetists were inactive (idle time). The more physical idle time occurs, the more it allows time for collecting of data from either the patient or the equipment. The most manual activities were contact with the patient and writing on the anaesthetic record, each of which required 6% of anaesthetic time. The anaesthetic record time ties in with the measurement of arterial pressure, being about 4% of the time, as they were usually carried out consecutively. The fact that there was little difference between the total visual recording activity and the plotting of the results would indicate that the records were infrequently used purely for reference purposes, but were mainly used for recording of events. Adjusting or altering the monitoring device occupied similar amounts of time, 5% of total manual time. However, below this level of activity, no other occurred for more than 2% of total time, with flow meter and vaporizer attention being close to this figure. There was little use of the anaesthetic reservoir bag for hand ventilation of the patient, which occupied only 0.4% of the time. (The

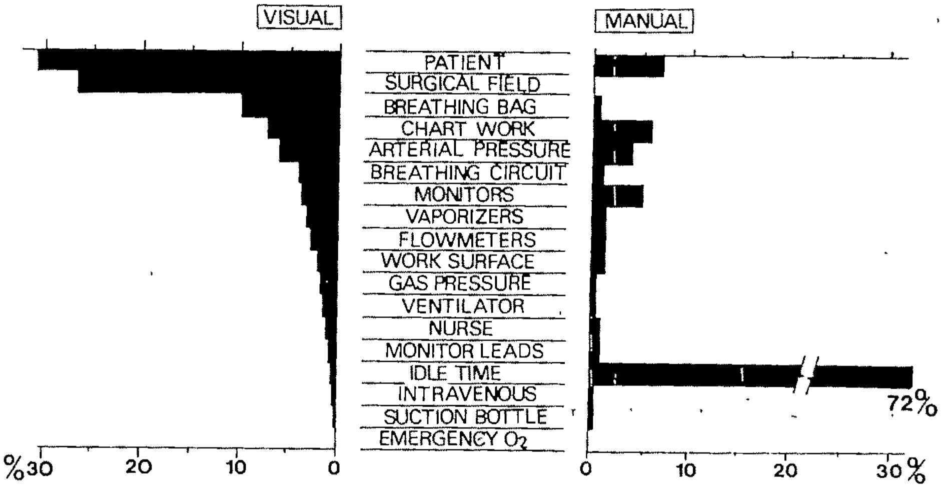


FIG. 1. The percentage of time taken by various visual and manual activities during the anaesthetics filmed.

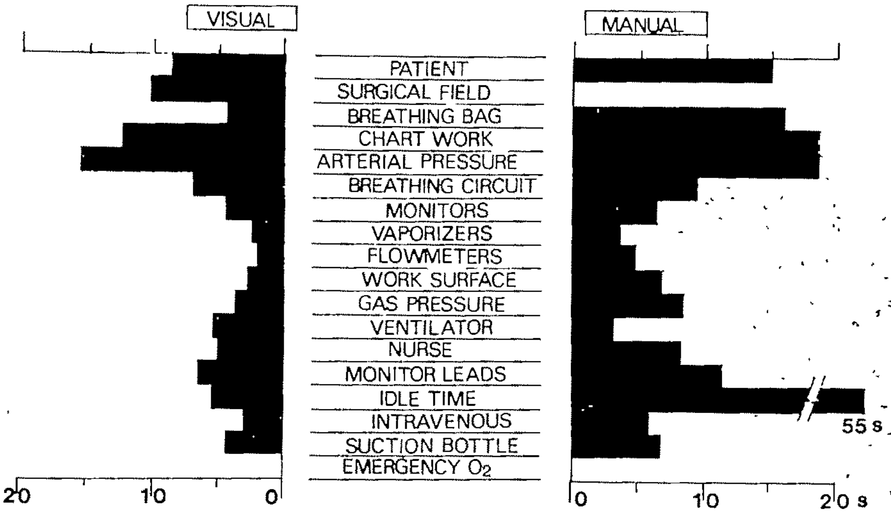


FIG. 2. The average duration of each visual and manual activity (s).

Northwick Park Hospital anaesthetic machine has a built-in ventilator.) Time taken with monitoring gas pressure, visual and manual together, was also only about 2%. This result was affected by the one hospital having a pipe-line gas supply. Gas pressure was checked as often as the flow meters and vaporizers where a cylinder supply of gas was used.

(2) *The percentage of time for each activity in each quarter of the anaesthetic time*

Frequency percentage of activities was split into four quarters of the different times when activities or groups of activities occur. The majority of the displays, that is flow meters, vaporizers, monitors and the anaesthetic reservoir bag, were all checked less as the operation continued. This would seem to indicate either a decline in the need to check them or diminishing concentration. The quietest period, visually and manually, occurred in the third quarter of the anaesthetic. Visually, there was much more activity within the surgical field in this quarter, which would indicate a reduction in all the other activities or perhaps a concern in the progress of the operation. The last quarter showed a return to more activity, visual and manual, towards the patient and the machine work top, but a low percentage of activity with most of the control and display units. There was obviously more concern with control and display units during the first quarter, when the anaesthetist was anxious to ensure that he was in control of various functions. The anaesthetic record was used consistently for the first three-quarters, but there was a sudden decrease in use in the final quarter which was the result of the lack of activity in the third quarter or other activities being required as the anaesthetic ended.

(3) *The average duration of each activity* (fig. 2)

The results in this section did not prove as helpful as was hoped. The duration, visual and manual, ranged between 3 and 8 s, with few exceptions. Manual idle time had by far the longest average duration—55 s. There was a block of four manual activities which ranged from 15 to 19 s, these were measurement of arterial pressure, recording, manual ventilation and attention to the patient. Some of these activities are related, and if the duration of time spent between each could be decreased then there would be more time available for collecting vital data. The time spent looking at the breathing bag, vaporizers, flow meter and gas pressure was very short, between 2 and 5 s. This would indicate that there was a large number of separate observations. Therefore, the display and controls should be positioned so that the movements of the anaesthetist's eye and head are decreased as far as possible.

(4) *Importance of each activity* (fig. 3)

An importance rating was produced to complement the data on how long each activity occurred. Some individual activities may be highly important but used very occasionally. There were variations

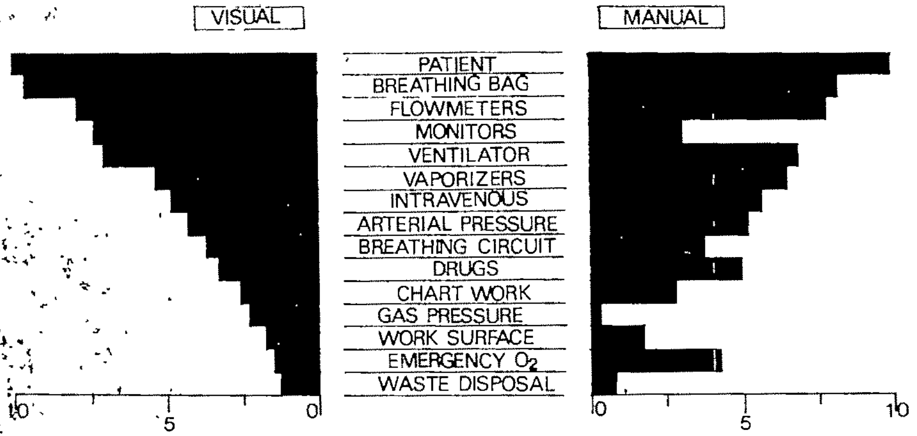


FIG. 3. The relative importance rating of visual and manual activities expressed in a score of 0 for no importance to 10 for greatest importance.

between different hospitals, because of the use of pipe-line or cylinder gas supply. Gas pressure and cylinders were given greater importance in the hospital with no pipe supply. The patient featured most in visual and manual activities. Visually, the four dynamic displays—that is, the reservoir bag, flow meters, monitors and ventilators—were the next important with least attention being paid to the vaporizer, probably because the vaporizer control is a static display. The rating of manual activities followed the same basic pattern, but the manual activity with the monitor was perhaps considered less important because it did not directly affect the patient. Also, the vaporizer adjustment was higher on the manual activity rating. The rating of importance of charts, manual and visual, was surprisingly low, but this may have been because they are used for recording facts which were used principally in a retrospective manner with regard to the care of the patient. Emergency oxygen control was rated low visually, but the manual rating was thought quite important. The disposal of rubbish and soiled apparatus was given little importance in rating; this is surprising.

(5) *The frequency of connection between visual and manual activities*

The interface value was a study of the sequence of activities to find out what activities occurred in relation to each other. There was generally much less manual than visual movement from one activity to another. However, certain manual movements do stand out. By far the strongest relationship was between the sphygmomanometer and the chart, a sequence which occurred continually throughout the anaesthetic. There was also a tendency to alter the vaporizer setting after altering the flowmeter, and there was a relation between the activities involving the patient, anaesthetic circuit and work top. Generally, the same groups applied in respect of visual and manual activity, therefore the interface study suggests the positioning of apparatus can be modified to be more efficient. The most notable connected visual movement was between the patient, surgeon and reservoir bag. Secondary visual activity was directed to the displays such as gas pressure, flow meters, vaporizers and monitors which were viewed in different orders (fig. 4).

DESIGN CONCLUSIONS

The results described were the more obvious and, possibly, more important. The information that can be obtained from the data is greater than was used in the present design. It was accepted that there may have been flaws in the methods used concerning, for instance, the number of hours filmed and the number of anaesthetists questioned and evaluated.

However, with the limits of time and equipment available it was felt that a reasonable sample was studied. The design conclusions that were drawn from this work were:

(1) A better organized arrangement for control and display units could be used to relate to the anaesthetist's working situation.

(2) A rationalization of the specific needs of work surface and storage could be envisaged.

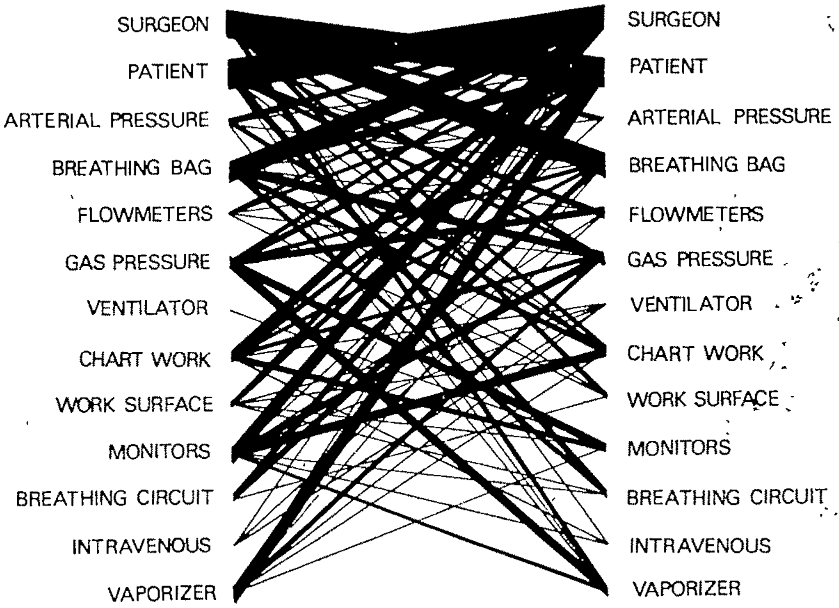


FIG. 4. The thickness of connecting lines indicates the frequency of the anaesthetists' eye movements directly from one object to another while giving anaesthetics.

(3) A rationalization of the inter-relationship of pieces of equipment is possible.

(4) Adaptability is essential to suit the different induction room and operating theatre requirements of individual anaesthetists.

These conclusions were then applied to a design by a process explained briefly below. First, sketches were made to study possible arrangements of control, display and work surface. These sketches were very schematic and more detailed ideas were then produced. Three systems, which covered the majority of possible arrangements, were studied. These were adaptation of the present system, a modular system and a work station system. From these ideas four full-sized cardboard mock-ups were produced of the anaesthetic work area and apparatus. These were then tried out functionally and shown to a number of anaesthetists and manufacturers whose comments and opinions were noted.

After rejection of some systems a more detailed mock-up was produced of the modularized system with a number of small variations and these were studied again. Because of the importance of control and display activities it was necessary to position them as close to the patient as possible without interfering with access to the patient. By splitting the control and display units into three modules positioned vertically, a compact system was produced with good display characteristics. The lowest module housed the gas pressure gauges, the flow meter and vaporizer controls. The middle module was the ventilator unit with the carbon dioxide absorber with its attached circuit and reservoir bag. The top module carried no gas flow and housed the electrocardiograph, the pulse monitor, respiration monitor and arterial pressure gauge. The reservoir bag, being the most checked visual display, was positioned close to the patient's head.

With the modules placed on top of each other, a slim unit was produced which occupied a relatively small surface area and could be positioned equally well on either side of the patient. An angled chart board was attached permanently to the unit because of the relationship between the arterial pressure gauge, monitors and chart work. The work surface and storage were treated separately because, apart from the chart work, the work surface activities had little direct relation to the control and display activities. Therefore, the work surface and storage units could be positioned to suit the individual anaesthetist's working arrangements (fig. 5). If required, the work surface unit could be attached to the control and display units to produce a complete traditional British style anaesthetic machine. The

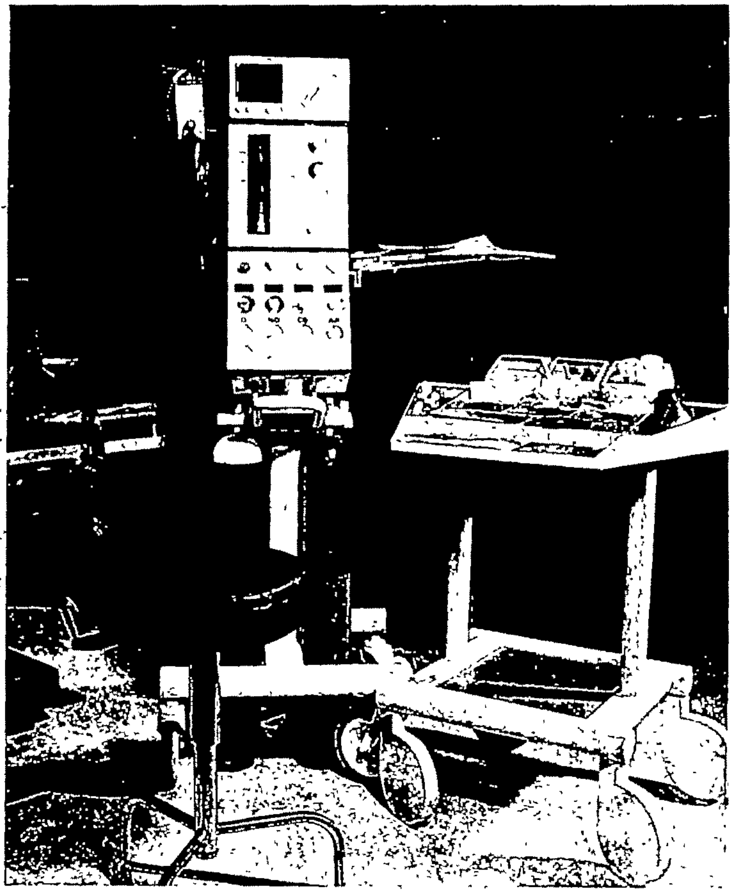


FIG. 5. A photograph of the model anaesthetic machine with vertical modules at the side of the head of the operating table with the adjacent work and storage units.

system would be equally suitable for pipe-line or cylinder gas supplies.

COMMENT

The present design of the anaesthetic machine has, to a great extent, evolved historically. There are, of course, various makes which differ slightly, but the majority of machines in Britain have the arrangement of the original Boyle's apparatus. Our ergonomic study was, of course, biased to a large extent by the fact that such apparatus was used. If the prototypes of new concepts (Cooper et al., 1978) could be studied in this way we may find that what we have now is what we are used to rather than the ideal.

As only one similar article on the subject in English is known to us (Drui, Belm and Martin, 1973) further study does seem indicated.

REFERENCES

Cooper, J. B., Newbower, R. S., Moore, J. W., and Tautman, E. D. (1978). A new anaesthesia delivery system. *Anesthesiology*, **49**, 310.

Drui, A. B., Belm, R. J., and Martin, W. E. (1973). Predesign investigation of the anesthesia operational environment. *Anesth. Analg. (Cleve.)*, **52**, 584.

MACHINE A ANESTHESIER—ETUDE DE SON FONCTIONNEMENT ET DE SA CONCEPTION

RESUME

Une étude ergonomique des activités routinières des anesthésistes a été faite à l'aide du matériel habituel. On a étudié en détails les films des mouvements manuels et visuels, puis on a enregistré les commentaires de certains spécialistes en anesthésie sur le matériel. Différents modèles d'appareils ont été utilisés pour évaluer leur acceptabilité. Le système modulaire a semblé préférable à un poste de travail ou à une adaptation des modèles actuels. On indique

dans cet article d'autres travaux à effectuer ainsi que la marche à suivre pour la construction de prototypes dans le but de moderniser la machine à anesthésier.

DIE MASCHINERIE DER ANÄSTHESIE—EINE FUNKTIONS- UND KONSTRUTIONSSTUDIE

ZUSAMMENFASSUNG

Eine Zeitstudie der Routineaktivitäten von Narkoseärzten wurde unter Verwendung konventioneller Gerate durchgefuhrt. Filme manueller und visueller Bewegungen wurden genau studiert, und die Erwartungen bestimmter beratender Narkoseärzte im Hinblick auf Apparate wurden aufgezeichnet. Modelle von Apparaten wurden zur Überprüfung ihrer Akzeptierbarkeit benutzt. Ein Modulsystem schien einer Arbeitsstation oder einer Adaptierung vorhandener Konstruktionen vorzuziehen zu sein. Weitere Untersuchungen und die Konstruktion von Prototyp-Apparaten scheint erforderlich zu sein, wenn die Anästhesie-Maschinerie modernisiert werden soll.

LA MAQUINA ANESTETICA—UN ESTUDIO DE SU FUNCION Y DISEÑO

SUMARIO

Se llevó a cabo un estudio de tiempo y moción de las actividades rutinarias del anestesista al usar el equipo convencional. Se estudiaron las películas de los movimientos visuales y manuales en detalle y se registraron las expectativas de ciertos anestesistas consultores respecto de los aparatos. Se realizaron pruebas con modelos del aparato para comprobar su aceptabilidad. Un sistema modular pareció ser preferible para una estación de trabajo o para su adaptación al diseño actual. Será necesario llevar a cabo mayores trabajos y construir prototipos si se quiere modernizar la máquina anestetica.

Br. J. Anaesth. (1980), **52**, 69

NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE IN ANAESTHETIZED MAN

J. P. PAYNE, R. HUGHES AND S. AL AZAWI

SUMMARY

The tetanic and single twitch responses of the adductor pollicis muscle were used to study the neuromuscular effects of neostigmine in 26 patients anaesthetized with thiopentone and nitrous oxide. Neostigmine 2.5 mg i.v. given 5 min after exposure to halothane antagonized non-depolarizing neuromuscular block, whereas a second dose given 2–5 min later depressed the peak tetanic contraction and re-established tetanic fade. In the absence of halothane the second dose of neostigmine had less effect. Recovery of the single twitch was not impaired by the second dose. A single dose of neostigmine 5 mg rapidly antagonized the competitive block of the tetanic response but the subsequent slight depression of the peak contraction and the brief reappearance of fade were less than after 5 mg given in two doses of 2.5 mg. In patients who were not given neuromuscular blocking drugs, one or two injections of neostigmine 2.5 mg caused a substantial reduction in the peak tetanic contraction and severe tetanic fade which persisted for about 20 min; the single twitch was slightly potentiated. The neostigmine block of the tetanic response could be antagonized by gallamine and potentiated by suxamethonium. These findings indicate that neostigmine in clinical doses can produce an acetylcholine-induced block which would be a potential hazard in anaesthetic practice.

Although the potential neuromuscular blocking properties of neostigmine have been known for many years (Briscoe, 1936; Goodman and Gilman, 1956; Blaber and Bowman, 1963), no quantitative assessment of this effect has been described in man. In a previous study we demonstrated that halothane potentiated the neuromuscular block caused by non-depolarizing drugs and that it was reversed by neostigmine (Hughes and Payne, 1979). However, we also found that although the block was antagonized by a first dose of neostigmine, a subsequent dose of the anticholinesterase enhanced the block.

Accordingly, we decided that this interesting observation deserved further investigation and the present work was undertaken to obtain a quantitative assessment of this drug interaction in man.

METHODS

Studies were performed, after informed consent had been obtained, on 26 patients about to undergo elective urological surgery. No premedication was given and anaesthesia was induced with thiopentone 300–600 mg i.v.; some patients were also given halothane 2–4%. Intubation of the trachea was performed without the use of a neuromuscular blocking agent after the larynx had been sprayed with lignocaine 4%. Where appropriate, halothane was then discontinued and anaesthesia maintained with a mixture of nitrous oxide 60–75% in oxygen given by intermittent positive pressure ventilation; supplements of thiopentone 100–200 mg and pethidine 50–150 mg were given as required. Simultaneous recordings of tetanic and single twitch contractions of the adductor pollicis muscles were made as described previously (Sugai, Hughes and Payne, 1975). Each ulnar nerve was stimulated supramaximally at the wrist every 12 s with rectangular pulses of 200 μs duration, one nerve at 50 Hz for 1 s and the other with single pulses.

In one series of experiments halothane 2% was administered after i.v. neuromuscular blocking doses of tubocurarine 0.1–0.24 mg kg^{-1}, dimethyl tubocurarine 0.075–0.1 mg kg^{-1} and gallamine 1.0–1.6 mg kg^{-1} when recovery of the tetanic response had reached 50%. After 5 min when the peak height of the tetanic contraction was reduced and tetanic fade was increased by halothane, neostigmine 2.5 mg was given i.v. preceded by atropine 1.2 mg. Two to five minutes later, while the administration of halothane continued, a second dose of neostigmine 2.5 mg

---

J. P. PAYNE, M.B., F.F.A.R.C.S., D.A.; R. HUGHES,* B.SC., M.SC., PH.D.; S. AL AZAWI, M.B., CH.B., F.F.A.R.C.S.I., Research Department of Anaesthetics, Royal College of Surgeons of England, London WC2 and St Peter's Hospitals, London WC2.

* Present address: Pharmacology Department, The Wellcome Research Laboratories, Langley Court, Beckenham, Kent.

0007–0912/80/010069–08 $01.00

© Macmillan Journals Ltd 1980

was given. Groups of three patients were used for each neuromuscular blocking drug studied.

In a second series of experiments halothane was omitted and the first dose of neostigmine was administered when recovery from neuromuscular blockade had reached 50%; a second dose of neostigmine was administered 2 min later. Groups of two patients were used for each neuromuscular blocking drug studied.

Similarly, two patients received a single i.v. dose of neostigmine 5 mg, preceded by atropine 1.2 mg, one during recovery from neuromuscular paralysis by dimethyl tubocurarine 0.075 mg kg^{-1} and the other after gallamine 1.0 mg kg^{-1} when paralysis had been enhanced by halothane 2%.

Finally, nine patients, who were not given neuromuscular blocking agents, received up to three i.v. injections of neostigmine 2.5 mg preceded by atropine 1.2 mg. Four of these patients were subsequently given gallamine 10 mg i.v. and two patients received suxamethonium 0.3 mg kg^{-1}.

RESULTS

In each group of three patients simultaneous recordings of the tetanic and twitch responses showed that after tubocurarine, dimethyl tubocurarine and gallamine, administration of halothane 2% caused an immediate increase in tetanic fade with a reduction in the peak height of the tetanic contraction. These effects were readily antagonized by neostigmine 2.5 mg i.v., but reappeared and were often enhanced by a second dose of anticholinesterase given 2–5 min later while the administration of halothane was continued (fig. 1). Recovery of the twitch response was unaffected by halothane; it was usually maximal when the first dose of neostigmine was given, and was not impaired by the second dose. Recordings taken at the same time, but at a faster paper speed, show more clearly the effects on tetanic fade (fig. 2).

Similar effects with neostigmine were obtained during recovery from neuromuscular blockade by tubocurarine, dimethyl tubocurarine and gallamine

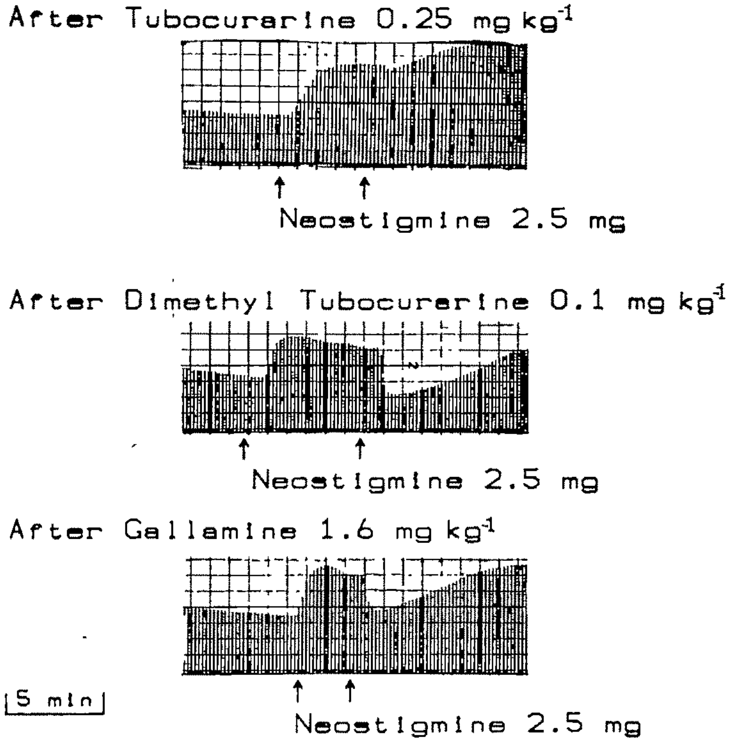


FIG. 1. Tracings from three anaesthetized patients showing the increase in peak tetanic contraction when neostigmine 2.5 mg, preceded by atropine 1.2 mg, was given in the presence of halothane 2% after neuromuscular blockade by tubocurarine, dimethyl tubocurarine and gallamine, and the decrease in the peak tetanic contraction following a second dose of neostigmine given 3–5 min later.

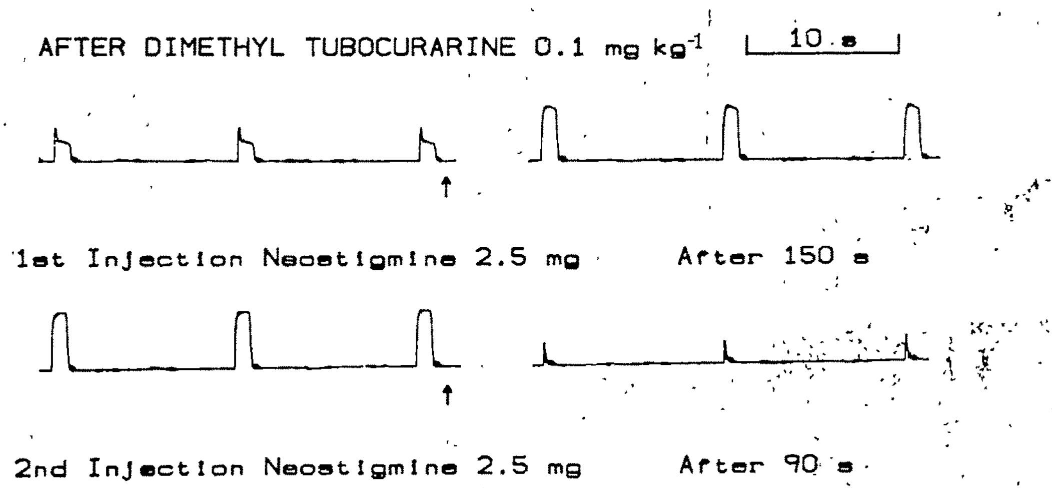


FIG. 2. Tracing from an anaesthetized patient recorded at a faster paper speed showing that, after neuromuscular blockade by dimethyl tubocurarine and in the presence of halothane 2%, a first dose of neostigmine 2.5 mg restored the peak height of the tetanic contraction and abolished the fade, whereas following a second dose of neostigmine given 5 min later the peak height was greatly reduced and the tetanic fade was virtually complete.

in the absence of halothane. Groups of two patients were used for each drug.

Tetanic fade is defined as the rapid "fall off" of the tetanus from the peak height to a level at which it "holds" until the end of the stimulus. Our method of obtaining a quantitative assessment of this effect has already been described (Hughes and Payne, 1979).

The mean results obtained in the three groups of three patients who also received halothane 2% are summarized in table I. In each patient and for each neuromuscular blocking drug studied, the first dose of neostigmine restored the peak contraction height and abolished the tetanic fade, whereas a second dose of neostigmine given 2–5 min later reduced the peak contraction and re-established the tetanic fade.

Similarly, in those patients who were not given halothane (table II) the first dose of neostigmine was antagonistic. However, the depression of the peak contraction height and the extent of the tetanic fade following a second dose of neostigmine was usually less than in those patients who received halothane 2%.

In one patient, a single dose of neostigmine 5 mg was given after a neuromuscular blocking dose of gallamine 1.0 mg kg^{-1} in the presence of halothane. Although an immediate antagonism occurred, some tetanic fade (21%) with a slight depression of the peak contraction was evident about 4 min after the administration of neostigmine. Another patient given a single dose of neostigmine 5 mg during recovery from neuromuscular blockade by dimethyl tubocurarine 0.075 mg kg^{-1} in the absence of halothane showed a similar response (fig. 3); again, the rapid antagonism of the tetanic response was followed by a transient reduction in peak height. The lower tracing recorded at a faster speed shows the brief

TABLE I. *Effects on the tetanic responses of the adductor pollicis muscle of two doses of neostigmine 2.5 mg given after neuromuscular blockade by tubocurarine, dimethyl tubocurarine and gallamine and during exposure to halothane 2%. Mean values are quoted with standard deviations in groups of three anaesthetized patients for each drug*

Drug	Dose (mg kg^{-1}) i.v.	1st dose neostigmine 2.5 mg		2nd dose neostigmine 2.5 mg	
		Peak contraction (% initial)	Tetanic fade (%)	Peak contraction (% initial)	Tetanic fade (%)
Tubocurarine	0.1–0.24	170 ± 21.9	0	79 ± 14.6	71 ± 6.9
Dimethyl tubocurarine	0.075–0.1	169 ± 9.8	0	54 ± 9.3	68 ± 22
Gallamine	1.0–1.6	191 ± 20	0	79 ± 13.9	71 ± 21.5

TABLE II. *Effects on the tetanic responses of the adductor pollicis muscle of two doses of neostigmine 2.5 mg given during recovery from neuromuscular blockade by tubocurarine, dimethyl tubocurarine and gallamine in groups of two anaesthetized patients for each drug. Mean values are quoted with individual results in parentheses*

Drug	Dose (mg kg^{-1}) i.v.	1st dose neostigmine 2.5 mg		2nd dose neostigmine 2.5 mg	
		Peak contraction (% initial)	Tetanic fade (%)	Peak contraction (% initial)	Tetanic fade (%)
Tubocurarine	0.1–0.15	169 (166, 171)	0	95 (94, 95)	22 (21, 22)
Dimethyl tubocurarine	0.075	143 (136, 150)	0	65 (46, 84)	49 (29, 68)
Gallamine	0.75	165 (152, 177)	0	96 (96, 96)	2 (2, 2)

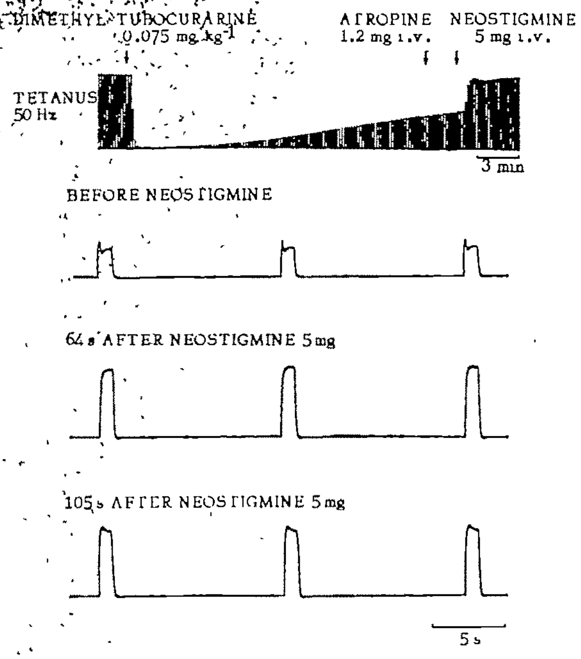


FIG. 3. Tracings from an anaesthetized patient recorded at slow and fast paper speeds showing that a single dose of neostigmine 5 mg preceded by atropine 1.2 mg given during recovery from neuromuscular blockade by dimethyl tubocurarine rapidly antagonized the tetanic response, but this was followed by a transient reduction of its peak height with a brief reappearance of some tetanic fade.

reappearance of some tetanic fade. The single twitch (not illustrated) showed only the initial antagonism. However, in both instances, the blockade produced by a single dose of neostigmine 5 mg was less than that produced by two doses of 2.5 mg.

A final group of nine patients, who were not given neuromuscular blocking drugs, received up to three injections of neostigmine 2.5 mg. In five patients a single injection of neostigmine 2.5 mg was sufficient to block the tetanic response partially. In the remaining four patients a second dose of neostigmine 2.5 mg was required to produce a substantial reduction in the peak height of the tetanic response which persisted for about 20 min. A typical recording is seen in figure 4. The lower tracing recorded at a fast speed shows that the degree of fade was so marked that the tetanic response was virtually, converted to a single twitch. The single twitch itself (not shown) was unimpaired and in fact was slightly enhanced. In two of these four patients a third injection of neostigmine was given with a scarcely perceptible additional effect.

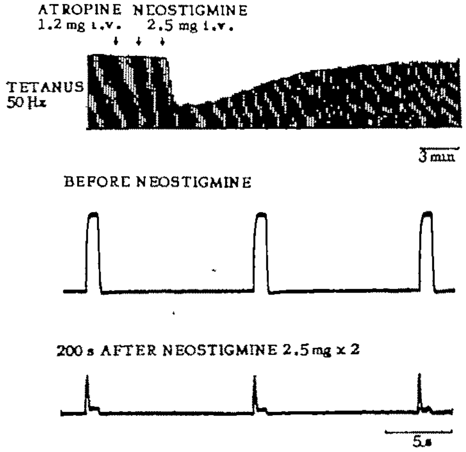


FIG. 4. Tracings from an anaesthetized patient recorded at slow and fast paper speeds showing the neuromuscular block and very marked tetanic fade which occurred after two doses of neostigmine 2.5 mg preceded by atropine 1.2 mg

A further important observation was that gallamine antagonized the block caused by neostigmine. This

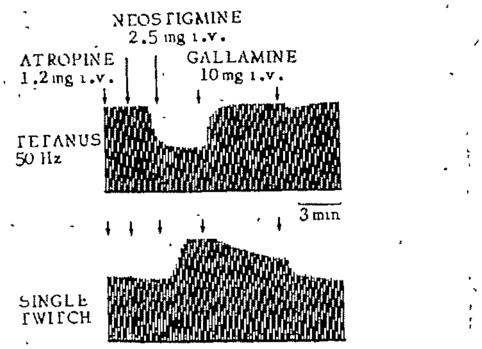


FIG. 5. Tracings from an anaesthetized patient showing neuromuscular block of the tetanic response after two doses of neostigmine 2.5 mg, preceded by atropine 1.2 mg, and the potentiation of the single twitch. Gallamine 10 mg antagonized the neuromuscular block of the tetanic response and reversed the potentiation of the single twitch.

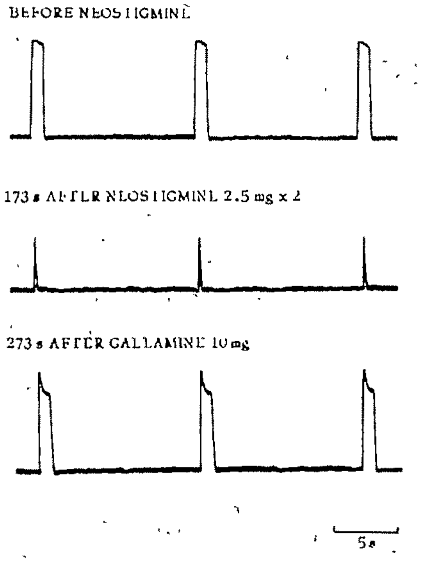


FIG. 6. This recording, taken simultaneously as that shown in figure 7 but at a faster paper speed, shows that the complete tetanic fade which occurred after the two doses of neostigmine 2.5 mg was almost entirely abolished by gallamine 10 mg.

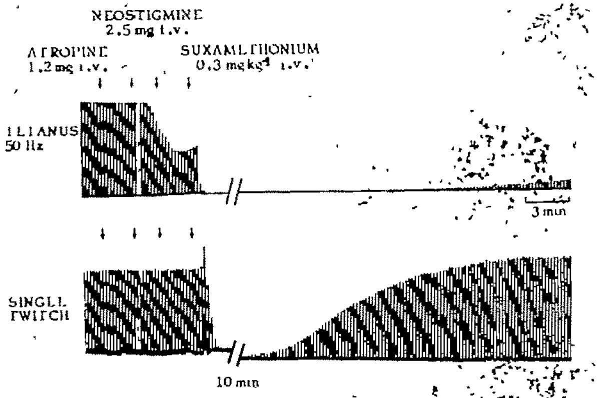


FIG. 7. Recordings from an anaesthetized patient showing that blockade of the tetanic response by two doses of neostigmine 2.5 mg was potentiated by suxamethonium 0.3 mg kg^{-1}; fasciculations occurred on the single twitch.

effect was seen in all four patients who were given the drug in the presence of neostigmine block (fig. 5). The first dose of neostigmine 2.5 mg produced a reduction in the peak contraction of the tetanic response which became more marked after a further dose of 2.5 mg; the single twitch was potentiated. Blockade of the tetanic response was rapidly antagonized by gallamine 10 mg, whereas a further dose of 10 mg produced a small transient depression. In contrast, the two doses of gallamine 10 mg progressively reversed the initial potentiation of the single twitch. Figure 6, recorded at faster speed, shows that the complete tetanic fade which occurred after the two doses of neostigmine 2.5 mg was almost entirely abolished by gallamine 10 mg. Finally, two patients in this group were given suxamethonium 0.3 mg kg^{-1} after neuromuscular block had been established with neostigmine. In both instances the block of the tetanic response was potentiated by suxamethonium (fig. 7) and in each case the subsequent recovery was slow. Fasciculations preceded the block on the single twitch which recovered more slowly than normal.

DISCUSSION

These studies in anaesthetized man have substantiated the early work of Briscoe (1936, 1937) who showed in cats that neostigmine and physostigmine rapidly depressed the muscle responses to high rates of stimulation and that these muscle responses became twitch-like in character. Furthermore, Briscoe (1938) also reported that these effects of anticholinesterase drugs could be abolished by curare and our observation that gallamine will reverse neostigmine block confirms her claim.

In our studies neostigmine was given to one group of patients in whom the recovery from neuromuscular block by non-depolarizing drugs had been reversed by exposure to halothane. In these patients paralysis of the tetanic responses of the adductor pollicis muscle was antagonized by a first dose of neostigmine 2.5 mg, whereas a second dose, given a few minutes later, reduced the peak height of the tetanic contraction and produced tetanic fade. The study was repeated without halothane when a second dose of neostigmine was usually less effective than in those patients who were also receiving halothane. This difference is not surprising because we have demonstrated previously that halothane itself, in the presence of a competitive blocking agent, will depress the peak tetanic contraction and increase tetanic fade (Hughes and Payne, 1979).

The question then arose whether or not a single dose of neostigmine 5 mg would produce a similar effect as the same amount in two doses of 2.5 mg when given during recovery from blockade by competitive agents and in the presence or absence of halothane. In both instances, after the immediate antagonism by neostigmine 5 mg, there was a transient reduction in the peak height of the tetanic contraction and a brief reappearance of tetanic fade. However, these effects were substantially less than those produced by 5 mg given in two doses of 2.5 mg.

Since the neuromuscular paralysing action of neostigmine in the presence of a competitive blocking agent was more marked when given in divided doses, it is possible that the tetanic response had fully recovered after the first dose of neostigmine 2.5 mg, so that the second dose was acting on normal unblocked muscle. When this hypothesis was tested in patients who were not given neuromuscular blocking drugs, one or two doses of neostigmine 2.5 mg produced a substantial reduction in the peak height of the tetanic contraction which persisted for about 20 min. The tetanic fade was so marked that this response had now virtually become a single twitch. Furthermore, we found that the neostigmine block could be antagonized by a small dose of gallamine and potentiated by suxamethonium, the action of which was also prolonged. These findings provide evidence that neostigmine, in sufficient dosage, will produce an acetylcholine-induced block of the tetanic response in anaesthetized man. The preserved acetylcholine will accumulate at the muscle end-plate and produce a depolarization block.

Tetanic fade produced by anticholinesterases is associated with a marked inhibition of acetylcholinesterase (Barnes and Duff, 1953). The end-plate potentials are prolonged and during high frequency nerve stimulation they summate and block the neuromuscular function by a persistent depolarization of the postsynaptic membrane. It is worth noting that anticholinesterase drugs also have a facilitatory action on the motor nerve terminal (Riker and Standaert, 1966) which would further increase the acetylcholine available at the muscle end-plate. Furthermore, it is likely that such prejunctional events would be more evident when the motor nerve terminals are fully activated and when the acetylcholine reserves are fully mobilized as during tetanic stimulation. It is also possible that an initial excessive release of acetylcholine produced by an anticholinesterase drug would rapidly exhaust the available transmitter which may in part account for the transmission failure (Blaber and Bowman, 1963). No doubt each of these factors contributed to our observation that neostigmine depressed the peak tetanic contraction and caused severe tetanic fade in anaesthetized man.

In contrast, it was intriguing that the responses of the single twitch were in fact potentiated by one or two doses of neostigmine 2.5 mg and that gallamine restored the single twitches to their initial contraction height. This feature illustrates the genuine differences between the tetanic and single twitch responses. The potentiation of the single twitch response by neostigmine may be explained by the fact that anticholinesterase drugs at low frequencies of stimulation produce a short burst of muscle action potentials (repetitive firing) so that the muscle now responds as if stimulated at a higher frequency and the twitch tension increases (Brown, Dale and Felding, 1936; Brown, 1937). The increased availability of acetylcholine at the muscle end-plate, mainly as a result of inhibition of acetylcholinesterase and partly as a result of an increased release of the transmitter from the motor nerve terminals, would augment and prolong the end-plate potentials and lead to repetitive firing of the muscle fibres as described by Eccles, Katz and Kuffler (1942). However, the amount of acetylcholine available, unlike that after high frequency tetanic stimulation, is insufficient to produce a depolarizing neuromuscular block. Nevertheless, it must be emphasized that tetanic stimulation provides the more physiological response since breathing and contractions of skeletal muscles are activated by tetanic trains of stimuli rather than by single pulses.

It is not immediately clear why gallamine should antagonize the neuromuscular blocking action of neostigmine, but the fact that the fade in the tetanic response was so rapidly reversed by gallamine might imply that the drug was competing with the excess acetylcholine for the appropriate receptors and this interpretation is supported, if the earlier argument is accepted, by the restoration to control height of the intensified twitch response, and the enhancement of the neostigmine block by suxamethonium gives further substance to this explanation.

It may be concluded from our results that neostigmine, in clinical doses, could be a potential hazard in anaesthetic practice. Obviously, the critical factors are the total dose of neostigmine administered and the degree of recovery achieved when the drug is given to reverse paralysis. Clearly, if recovery of the tetanic response has reached about 50%, then a single 2.5-mg dose should be sufficient to provide adequate reversal. If a larger dose of neostigmine is required for complete antagonism of a deeper block, then a single dose of 5 mg may be preferable to two doses of 2.5 mg.

However, when full recovery has been achieved, a further dose of neostigmine 2.5 mg could be hazardous because a prolonged depolarizing block with apnoea could ensue. Moreover, it is possible that instances of residual curarization after apparent inadequate reversal may have been attributable to overdosage with neostigmine.

ACKNOWLEDGEMENTS

We are indebted to Miss V. A. Bishop, S.R.N., Mr D. Knox, B.TECH. and Mr A. J. Harman for skilled technical assistance, to our surgical and nursing colleagues for their tolerance and patience and to our volunteers without whom this study would not have been possible.

REFERENCES

Barnes, J. M., and Duff, J. I. (1953). The role of cholinesterase at the myoneural junction. *Br. J. Pharmacol.*, **8**, 334.

Blaber, L. C., and Bowman, W. C. (1963). Studies on the repetitive discharges evoked in motor nerve and skeletal muscle after injection of anticholinesterase drugs. *Br. J. Pharmacol.*, **20**, 326.

Briscoe, G. (1936). Shift in optimum rate of stimulation due to prostigmine. *J. Physiol.* (*Lond.*), **86**, 48P.

—— (1937). Optimum stimulation rates for red and white skeletal mammalian muscles, and shift in rates produced by the eserine group. *J. Physiol.* (*Lond.*), **90**, 10P.

—— (1938). Changes in muscle contraction curves produced by drugs of the eserine and curarine groups. *J. Physiol.* (*Lond.*), **93**, 194.

Brown, G. L. (1937). Action potentials of normal mammalian muscle. Effects of acetylcholine and eserine. *J. Physiol.* (*Lond.*), **89**, 220.

—— Dale, H. H., and Feldberg, W. (1936). Reactions of normal mammalian muscle to acetylcholine and to eserine. *J. Physiol.* (*Lond.*), **87**, 394.

Eccles, J. C., Katz, B., and Kuffer, S. W. (1942). Effect of eserine on neuromuscular transmission. *J. Neurophysiol.*, **4**, 402.

Goodman, L. S., and Gilman, A. (1956). *The Pharmacological Basis of Therapeutics*, 2nd edn, p. 451. New York: Macmillan.

Hughes, R., and Payne, J. P. (1979). Interaction of halothane with non-depolarizing neuromuscular blocking drugs in man. *Br. J. Clin. Pharmacol.*, **7**, 485.

Riker, W. F., and Standaert, F. G. (1966). The action of facilitatory drugs and acetylcholine on neuromuscular transmission. *Ann. N.Y. Acad. Sci.*, **135**, 163.

Sugai, N., Hughes, R., and Payne, J. P. (1975). The effect of suxamethonium alone and its interaction with gallamine on the indirectly elicited tetanic and single twitch contractions of skeletal muscle in man during anaesthesia. *Br. J. Clin. Pharmacol.*, **2**, 391.

BLOCAGE NEUROMUSCULAIRE APRES ADMINISTRATION DE NEOSTIGMINE CHEZ LES ANESTHESIES

RESUME

Les réactions tétaniques et de contraction unique du muscle adducteur du pouce ont servi à l'étude des effets neuromusculaires de la néostigmine sur 26 patients anesthésiés à l'aide de thiopentone et de protoxyde d'azote. L'administration intraveineuse de 2,5 mg de néostigmine après exposition à l'halothane a été à l'encontre du blocage neuromusculaire non dépolarisant, alors qu'une seconde dose administrée entre 2 et 5 min plus tard a déprimé la contraction tétanique de crête et rétabli le "fading" tétanique. Sans halothane, la seconde dose de néostigmine a eu moins d'effet. La récupération à la suite de la contraction unique n'a pas été affectée par la second dose. Une seule dose de 5 mg de néostigmine s'est rapidement opposée au blocage compétitif de la réaction tétanique, mais la légère dépression ultérieure de la contraction de crête et la brève réapparition de "fading" ont été moins prononcées qu'après l'administration de 5 mg en deux doses de 2,5 mg. Chez les patients n'ayant pas reçu d'agents de blocage neuromusculaire, une ou deux injections de 2,5 mg de néostigmine ont considérablement réduit la contraction tétanique de crête mais causé un "fading" tétanique grave qui a duré pendant environ 20 min; la contraction unique a été légèrement activée. Le blocage de la réaction tétanique par la néostigmine peut être opposé par la gallamine et activé par le suxaméthonium. Les résultants de ces études font ressortir que la néostigmine administrée en doses cliniques peut être à l'origine d'un blocage provoqué par l'acétylcholine, lequel pourrait présenter un risque éventuel en anesthésie.

NEUROMUSKULÄRE BLOCKIERUNG DURCH NEOSTIGMIN BEI NARKOTISIERTEN MENSCHEN

ZUSAMMENFASSUNG

Die tetanische und die Einzel-Zuckreaktionen des Adductor pollicis-Muskel wurden zum Studium der neuromuskularen Effekte von Neostigmin bei 26 mit Thiopenton und Stickoxyd narkotisierten Patienten verwendet. Neostigmin (2,5 mg) wird intravenös nach Halothan verabreicht und hatten eine Gegenwirkung auf die nicht-depolarisierende neuromuskulare Blockierung, wogegen eine 2–5 min später verabreichte Dosis die tetanische Spitzenreaktion unterdruckte und ein tetanisches Absinken bewirkte. Bei

Abwesenheit von Halothan war die zweite Neostigmin-Dosis weniger wirksam, und Wiederherstellung der Einzelzuckung wurde dadurch nicht beeinträchtigt. Eine Dosis von 5 mg Neostigmin brachte eine schnelle Gegenwirkung gegen die Blockierung der tetanischen Reaktion, aber die folgende leichte Unterdruckung der Spitzenkontraktion und das kurze Wiederauftreten des tetanischen Absinkens waren geringer als nach einer Verabreichung von 5 mg in zwei Einzeldosen zu 2,5 mg. Bei Patienten, die keine Drogen zur neuromuskulären Blockierung erhalten hatten, bewirkten eine oder zwei Injektionen von Neostigmin (2,5 mg) eine wesentliche Verringerung der tetanischen Spitzenreaktion und schweres tetanisches Absinken auf etwa 20 min; die Einzelzuckung war leicht verstärkt. Die Neostigmin-Blockierung der tetanischen Reaktion konnte durch Gallamin aufgehoben und durch Suxamethonium verstarkt werden. Diese Resultate zeigen an, dass Neostigmin in klinischen Doseneine durch Azetylcholin bewirkte Blockierung hervorrufen kann, die eine potentielle Gefahr in der Narkosepraxis bedeuten kann.

BLOQUEO NEUROMUSCULAR POR NEOSTIGMINA EN HOMBRE ANESTESIADO

SUMARIO

Se usaron las respuestas contraccional única y tetánica del músculo aductor del pulgar para estudiar los efectos neuromusculares de la neostigmina en 26 pacientes anestesiados mediante tiopentona y óxido nitroso. Con 2,5 mg i.v. de neostigmina administrados después de la exposición al halotano, se antagonizó al bloqueo neuromuscular no-depolarizante, mientras que mediante una segunda dosis administrada 2–5 min después, se deprimió la contracción tetánica tope y se restableció la debilitación tetánica. Al no usarse halotano con la segunda dosis, ésta tuvo efectos menores. La recuperación de la contracción única no fue afectada negativamente por la segunda dosis. Una dosis única de 5 mg de neostigmina antagonizó rápidamente al bloqueo competitivo de la respuesta tetánica, pero la ligera depresión consecutiva de la contracción tope y la breve reaparición de la debilitación fueron menos fuertes que después de la administración de 5 mg en dos dosis de 2,5 mg cada una. En los pacientes a quienes no se administró substancias bloqueadoras neuromusculares, una o dos inyecciones de 2,5 mg de neostigmina causaron una reducción substancial de la contracción tetánica tope y una debilitación tetánica severa que duró por 20 min aproximadamente; aumentó la potencia de la contracción única de manera débil. Se podía antagonizar al bloqueo de la respuesta tetánica por neostigmina mediante galamina y aumentarlo con suxametonio. Estos resultados indican que la neostigmina en dosis clínicas puede producir un bloqueo inducido por acetilcolina, lo que constituiría un riesgo potencial en la anestesia.

Br. J. Anaesth. (1980), **52**, 77

COMPLEMENT-MEDIATED REACTIONS TO DIAZEPAM WITH CREMOPHOR AS SOLVENT (STESOLID MR)

M. S. HÜTTEL, A. SCHOU OLESEN AND E. STOFFERSEN

SUMMARY

Changes in complement reactions are described in two patients exhibiting adverse reactions to Stesolid MR (diazepam with Cremophor as solvent). The recorded frequency of adverse reactions to Althesin, propanidid and Stesolid MR suggests that the common solvent Cremophor is responsible for the adverse reactions.

It is known that i.v. injections of Stesolid (diazepam in glycoferol–alcohol–benzoic acid) frequently cause thrombophlebitis (Graham, Pagano and Conner, 1978). Assuming that the solvent system was responsible for this complication, Dumex Ltd (Copenhagen) produced an alternative formula of injectable diazepam. In this preparation (Stesolid MR) the original solvent system was replaced by a macrogol (Cremophor El) which resulted in a considerable decrease in the frequency of thrombophlebitis (Siebke, Ellertsen and Lind, 1976). Since 1976 we have used Stesolid MR as a sedative for endoscopy and our observations have confirmed that the preparation produces a smaller frequency of thrombophlebitis.

Unfortunately, the new preparation appears more liable to cause adverse systemic reactions. Following the administration of 5200 ampoules, we noted five anaphylactoid reactions three of which resulted in circulatory collapse (Schou Olesen and Hüttel, 1978). These episodes resembled immediate hypersensitivity reactions. However, one of the patients had not previously received Stesolid MR or any other diazepam preparation.

Watkins and others (1976) have shown that Althesin may activate complement C3 (alternative pathway) and since Althesin and Stesolid MR have the solvent Cremophor in common, we suspected that complement activation could cause the circulatory collapse. Since then we have had the opportunity to study another two patients who also developed adverse reactions to Stesolid MR.

METHODS

Venous blood was collected into tubes containing EDTA as soon as possible after the reaction and three further blood samples were collected over the next 24 h. A final sample was taken not sooner than 5 days after the incident to provide "baseline" values for the patient. Plasma was separated by centrifugation at 1500 *g* for 10 min and either analysed within 30 min or stored at −60 °C and then thawed immediately before analysis. This took place within 1 week after sampling. C1, C1q, C3 proactivator, C3 and C4 were estimated.

Analyses were performed by rocket immunoelectrophoresis as outlined by Laurell (1966), using monospecific antisera against C1 esterase inactivator, C3, C3 proactivator and C4 (Behringwerke A.G., Marburg, W. Germany). C1q was determined by Mancini radial immunodiffusion techniques (Mancini, Carbonara and Heremans, 1965) using the appropriate monospecific antiserum (Behringwerke). The degree of C3-conversion was estimated by two-dimensional immunoelectrophoresis (Axelsen, Krøll and Weeke, 1973) using C3 antiserum (Behringwerke).

RESULTS

The first patient was a 30-yr-old fit male with no history of allergy. Immediately after i.v. injection of Stesolid MR 10 mg he developed a diffuse rash on the face, neck and chest wall, rapidly followed by generalized rash. He complained of respiratory distress and bronchospasm developed. The radial pulse became weak, heart rate increased to 150 beat min^{-1} and the systolic arterial pressure was 40 mm Hg. He remained conscious and after treatment with oxygen by mask, hydrocortisone, metaoxidrine and theophylline i.v., his condition improved and the following day he was discharged in good health.

MOGENS S. HÜTTEL, M.D.; ANDERS SCHOU OLESEN, M.D.; ERIK STOFFERSEN, MED.TECH.; Department of Anaesthetics and Intensive Therapy, and Section of Blood Coagulation, Department of Clinical Chemistry, Aalborg Hospital, DK-9100 Aalborg, Denmark.

Correspondence to M. H.: Sdr. Boulevard 164, 31, DK-5000 Odense C, Denmark.

0007–0912/80/01077–03 $01.00

© Macmillan Journals Ltd 1980

C1, C1q and C4 showed minor variations (fig. 1) during the following 24 h and all were within normal range. The C3-activator concentration was found to be small although within normal range, while C3 was below the normal range and remained low compared with the "base-line" value. The immunochemical assay estimates both native C3 and $C3_c$ (the conversion product) as total C3, but two-dimensional immunoelectrophoresis revealed the preponderance of the electrophoretically faster $C3_c$ protein in the plasma immediately following the reaction (fig. 2). After 24 h only a small amount of $C3_c$ remained.

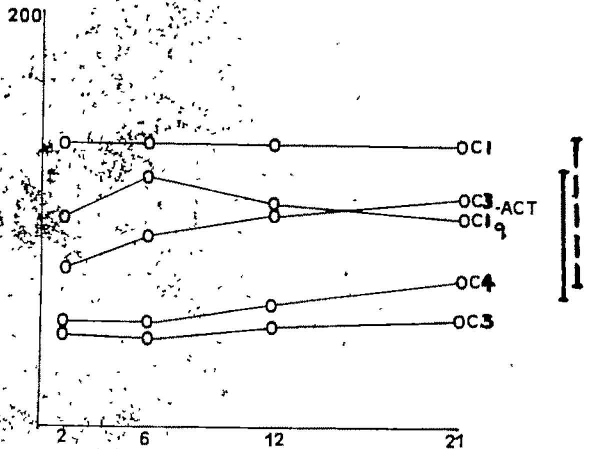


FIG. 1. Changes of complement factors in patient no. 1 (arbitrary units; C3 = mg dl^{-1}). I = Normal range for C3; I = normal range for C3-activator. C1, C1q and C4 within normal range.

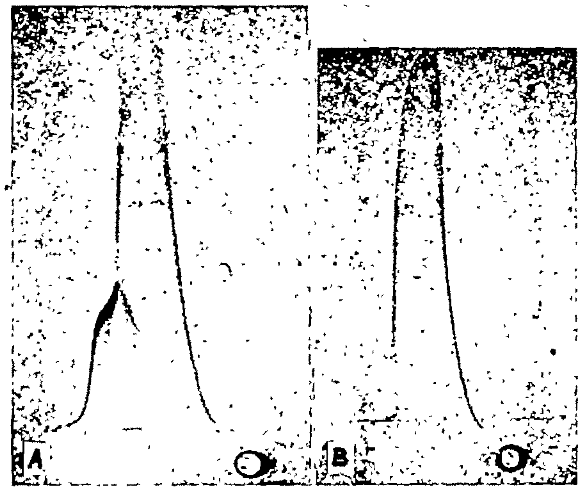


FIG. 2. Complement C3 patterns obtained by two-dimensional immunoelectrophoresis of the plasma from patient no. 1. Blood samples obtained (A) shortly after and (B) 24 h later from a patient exhibiting an immediate hypersensitivity reaction.

The second patient was a 32-yr-old previously healthy woman with no history of allergy. She had received Stesolid MR on a previous occasion without incident. Two minutes after an i.v. injection of Stesolid MR 10 mg she developed a generalized erythematous rash and complained of dizziness, abdominal pain and tingling of fingers and toes. A few minutes later facial oedema developed, the pulse became weak and the heart rate increased to 140 beat min^{-1}. Systolic arterial pressure decreased to 70 mm Hg. Breathing was normal and no bronchospasm was noted. Oxygen was given by mask and hydrocortisone 100 mg was administered i.v. She remained conscious and soon recovered apart from facial oedema, which persisted for 2 days.

There was no sign of C3 conversion in this patient. Complement was activated in a classical way, and these changes persisted for more than 24 hr. This may reflect an immune-mediated reaction with secondary complement involvement, since the patient had received Stesolid MR on a previous occasion.

DISCUSSION

Watkins, Ward and Appleyard (1977) have found that adverse reactions to Althesin seem to be predominantly mediated by complement C3 activation, although a small proportion of these reactions do appear to be immune-mediated (Watkins et al., 1976).

Reports of adverse reactions to diazepam have been extremely rare (Milner, 1977), but we have shown that Stesolid MR can activate C3 complement. The recorded frequency of adverse reactions to Althesin, propanidid and Stesolid MR (Schou Olesen and Hüttel, 1978) suggests the common solvent Cremophor is responsible for the adverse reactions. If this is verified, more acceptable solvents are required.

REFERENCES

Axelsen, N. H., Krøll, J., and Weeke, B. (1973). *A Manual of Quantitative Immunoelectrophoresis. Methods and Applications*, p. 47. Oslo–Bergen–Tromsø: Universitetsforlaget.

Graham, C. V., Pagano, R. R., and Conner, J. T. (1978). Pain and clinical thrombophlebitis following intravenous diazepam and lorazepam. *Anaesthesia*, **33**, 188.

Laurell, C. (1966). Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Analyt. Biochem.*, **15**, 45.

Mancini, G., Carbonara, A. O., and Heremans, J. F. (1965). Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochem.*, **2**, 235.

Milner, L. (1977). Allergy to diazepam. *Br. Med. J.*, **1**, 144.

Schou Olesen, A., and Hüttel, M. S. (1978). Circulatory collapse following intravenous administration of Stesolid MR. *Ugeskr. Laeg.*, **140**, 2644.

Siebke, H., Ellertsen, B. B., and Lind, B. (1976). Reactions to intravenous injections of diazepam. *Br. J. Anaesth.*, **48**, 1187.

Watkins, J., Clark, A., Appleyard, T. N., and Padfield, A. (1976). Immune-mediated reactions to Althesin (alphaxalone). *Br. J. Anaesth.*, **48**, 881.

—— Ward, A. M., and Appleyard, N. (1977). Adverse reactions to intravenous anaesthetic induction agents. *Br. Med. J.*, **2**, 1084.

REACTIONS ALEXINES-INTERMEDIAIRES AU DIAZEPAM AYANT LE CREMOPHOR COMME SOLVANT (STESOLID MR)

RESUME

On décrit dans cet article les changements qui ont eu lieu dans les réactions alexines de deux patients réagissant mal au Stesolid MR (diazépam ayant du Crémophor comme solvant). Etant donné la fréquence des réactions adverses enregistrées à l'Althésine, au propanidid et au Stesolid MR, il semblerait que le Crémophor, solvant commun dans chacun des cas, soit responsable de ces réactions.

KOMPLEMENT-REAKTIONEN AUF DIAZEPAM MIT CREMOPHOR ALS LÖSEMITTEL (STESOLID MR)

ZUSAMMENFASSUNG

Beschrieben werden Veränderungen der Komplement-Reaktionen bei zwei Patienten mit ungünstigen Reaktionen auf Stesolid MR (Diazepam mit Crémophor als Lösemittel). Aufzeichnugen über Häufigkeit solcher ungünstiger Reaktionen auf Althesin, Propanidid und Stesolid MR zeigen, dass das gewöhnliche Lösemittel Cremophor dafür verantwortlich ist.

REACCIONES DE COMPLEMENTO AL DIAZEPAM CON CREMOFOR COMO SOLVENTE (STESOLID MR)

SUMARIO

Se describen los cambios en las reacciones de complemento de dos pacientes en los cuales se advirtieron reacciones adversas al Stesolid MR (diazepam con cremofor como solvente). La frecuencia registrada de reacciones adversas al la Altesina, el propanidido y el Stesolid MR hace pensar que el solvente común—cremofor—es responsable por las reacciones adversas.

Br. J. Anaesth. (1980), **52**, 81

EFFECTS OF DOXAPRAM ON POSTOPERATIVE PULMONARY COMPLICATIONS FOLLOWING THORACOTOMY

P. S. SEBEL, E. J. KERSHAW AND W. S. RAO

SUMMARY

An i.v. solution of 5% dextrose with doxapram 2 mg ml^{-1} or 5% dextrose alone was administered to 53 patients following lateral thoracotomy. Estimations of arterial $P\mathrm{O}_2$, $P\mathrm{CO}_2$ and pH were made before operation, during infusion and 7 days after operation. Respiratory function tests were carried out before and 7 days after operation. There were no significant differences in arterial $P\mathrm{O}_2$, $P\mathrm{CO}_2$ and pH or in respiratory function tests between those who received doxapram and those who did not. In this study doxapram did not affect the frequency of postoperative pulmonary complications.

Doxapram hydrochloride is a respiratory stimulant which has an action both centrally and on the peripheral chemoreceptors (Kato and Buckley, 1964; Wang and Hirsch, 1973; Scott, Whitwam and Chakrabarti, 1977). The administration of doxapram has been shown to reduce respiratory complications and hypoxaemia in fit patients after abdominal surgery (Gupta and Dundee, 1974; Gawley, Dundee and Jones, 1975; Gawley et al., 1976; Downing et al., 1977). Lees and others (1976) suggested that reduction in hypoxaemia may be a result of a sparing effect on functional residual capacity (FRC). However, not all investigators agree that the drug is of value after surgery (Andersen and Krohg, 1976).

We have investigated the effects of an infusion of doxapram on postoperative pulmonary complications and on arterial $P\mathrm{O}_2$, $P\mathrm{CO}_2$ and pH in a group of patients with pre-existing lung disease undergoing lateral thoracotomy.

PATIENTS AND METHODS

Fifty-three patients admitted to the same surgical unit for thoracotomy gave informed consent to investigation. Patients with severe hypertension (> 112 mm Hg diastolic), severe coronary artery disease and those requiring repeat operation on the chest were excluded from the study.

Before operation arterial blood was sampled from the femoral or radial artery into a heparinized syringe with the patient breathing room air. The sample was analysed within 10 min for hydrogen ion activity ([H$^+$]), $P\mathrm{a}_{\mathrm{O}_2}$ and $P\mathrm{a}_{\mathrm{CO}_2}$ using a Corning pH/blood-gas 165 analyser previously calibrated using Corning buffer and calibration gas. Vital capacity (VC), the forced expiratory volume in 1 s (FEV$_1$) and the peak expiratory flow rates (PEF) were measured using a Vitalograph dry spirometer. The carbon monoxide transfer factor corrected for alveolar volume (K_{CO}) was measured by the single breath method using a P. K. Morgan Respirometer. A chest x-ray was taken before operation.

All patients were premedicated with papaveretum 10–20 mg and hyoscine 0.2–0.4 mg i.m. Anaesthesia was induced with a sleep dose of thiopentone. Following the administration of suxamethonium 100 mg, the trachea was intubated with an appropriate double-lumen tube. Ventilation was controlled throughout the operation with the aid of a non-depolarizing neuromuscular blocker and anaesthesia was maintained with a mixture of nitrous oxide in oxygen supplemented with fentanyl or phenoperidine. At the end of surgery, residual muscular paralysis was antagonized with neostigmine and atropine.

TABLE I. *Details of patients in the two groups*

	Doxapram	Control
Male	21	25
Female	3	4
Mean age (yr ± SD)	59.2 (11.09)	61.0 (11.16)
Operation		
Pneumonectomy	11	9
Lobectomy	7	8
No resection ± biopsy	4	8
Pleurectomy	2	4

P. S. SEBEL,* M.B., B.S., F.F.A.R.C.S.I.; E. J. KERSHAW, M.B., B.S., F.F.A.R.C.S.; W. S. RAO, M.D., F.F.A.R.C.S., D.A.; Brook Hospital, London, SE 18.

*Present address: Department of Anaesthetics, Wilhelmina Gasthuis, Academisch Ziekenhuis bij de Universiteit van Amsterdam, 1e Helmersstraat 104, Amsterdam, Holland.

0007–0912/80/010081–04 $01.00

© Macmillan Journals Ltd 1980

TABLE II. Arterial $P\mathrm{o}_2$, $P\mathrm{co}_2$ and acid–base data for the two groups. Mean values ±SD. Range in parentheses. 1 = Before operation; 2 and 3 = 2 h and 7 days after operation

	Doxapram ($n = 24$)			Control ($n = 29$)		
	1	2	3	1	2	3
[H$^+$] (nmol litre^{-1})	40.0±3.57 (38–44)	50.2±8.7	38.0±3.7	40.5±4.58 (32–54)	49.2±6.4	38.0±2.7
Pa_{CO_2} (kPa)	4.7±0.56 (3.9–5.6)	6.0±1.15	4.8±0.63	4.9±0.63 (4.0–6.4)	5.9±0.86	4.7±0.52
Pa_{O_2} (kPa)	10.6±0.56 (6.3–15.2)	13.0±4.08	9.8±1.74	10.6±1.99 (6.4–17.3)	14.8±4.39	9.6±1.54
Base excess (mmol litre^{-1})	−1.7±2.4 (−7 to +6.3)	−3.1±3.94	+0.1±2.8	−1.0±2.91 (−4.2 to +8)	−4.2±2.38	−0.7±3.17

TABLE III. *Respiratory function tests. See also legend to table II*

	Doxapram		Control	
	1	3	1	3
FEV$_1$ (litre)	2.7±1.23 (0.9–3.9)	1.8±0.75	2.6±0.91 (1.2–3.5)	1.8±0.68
VC (litre)	3.8±1.29 (2.3–5.8)	2.3±0.72	3.6±1.05 (1.7–5.2)	2.4±0.7
PEF (litre s^{-1})	6.6±2.36 (3.0–11.7)	4.9±2.1	6.7±1.98 (4.0–10.6)	5.1±1.43
K_{CO}	1.4±0.46 (0.3–2.2)	1.4±0.49	1.4±0.34 (0.8–2.0)	1.6±0.38

TABLE IV. *Cough and spit*

	No/slight cough	Cough and/or purulent sputum	%
Before operation			
Doxapram	19	4	21.0
Control	22	6	27.2
After operation			
Doxapram	22	1	4.5
Control	23	5	21.7

TABLE V. *Temperature data. See also legend to table II*

	Temp. (°C): mean ± SD		Temperature increase > 1 °C
	1	3	
Doxapram	36.4±0.57	36.5±0.37	2/21
Control	36.4±0.45	36.7±0.43	6/28

After operation, patients were randomly allocated to one of two groups. Group one (24 patients) received an infusion of doxapram 1000 mg in 500 ml 5% dextrose at the rate of 1 ml kg^{-1} h^{-1} (controlled by a Tekmar T51 infusion controller) for 6 h. Group two (29 patients) received the same quantity of 5% dextrose over the same period (table I). The two solutions were given in a double-blind manner.

Each patient was given oxygen 4 litre min^{-1} via a Hudson face-mask for 12 h. A sample of arterial blood was taken for estimation of arterial $P\mathrm{o}_2$, $P\mathrm{co}_2$ and [H$^+$] 2 h after the start of the infusion. All patients received ampicillin and flucloxacillin for 5–7 days. They also received physiotherapy (breathing exercises) twice a day for 3 days after operation, and then daily.

On the 7th day following operation, all the investigations carried out before operation were repeated.

RESULTS

Before surgery there were no significant differences between the two groups in respect of arterial $P\mathrm{o}_2$, $P\mathrm{co}_2$ or [H$^+$] or respiratory function.

Two hours after operation, Pa_{O_2}, Pa_{CO_2} and [H$^+$] were increased in both groups, but there were no significant differences between the groups. Neither was there any significant difference between the groups at 7 days (table II).

The respiratory function tests did not show any significant differences between the two groups (table III).

Taking production of purulent sputum or severe cough, or both, as evidence of respiratory infection, the doxapram group had a reduced frequency of infection although the difference between the groups was not statistically significant (table IV).

There was no significant difference in the number of patients who had an increase in temperature of more than 1 °C (table V).

The chest x-rays were reported by a radiologist who was unaware of the treatment group. He could detect no differences between the two groups.

Patients who underwent lobectomy showed some evidence of consolidation in the remaining lobe on the side of operation. Patients who underwent pneumonectomy, pleurectomy or who had no resection showed no evidence of collapse or consolidation that was not visible before operation.

During the study, one patient experienced facial sweating which was the only side-effect attributable to the administration of doxapram.

DISCUSSION

An infusion of doxapram 10 mg min^{-1} for 30 min following operation has been shown to cause an increase in Pa_{O_2}, and a decrease in Pa_{CO_2} (Downing et al., 1977). Gawley and others (1976), using a dose of 2 mg min^{-1} for 2 h found the increase in Pa_{O_2} to be sustained until the 5th day after surgery.

Lees and others (1976), who gave doxapram 250 mg over 2 h, found a significant increase in Pa_{O_2} only on the 1st day after operation and not subsequently.

In this study, doxapram was not effective as a pharmacological stimulus to breathing. It was used in a dose of 2 mg kg^{-1} h^{-1} for 6 h, which should have been long enough to outlast any residual respiratory depression from anaesthesia. This is the first study reporting the use of doxapram following surgery in patients with pre-existing lung disease, and in this group of patients it appeared to have had no effect on ventilation, as measured by Pa_{O_2} or Pa_{CO_2}.

The frequency of chest infections after abdominal surgery has been shown to be reduced by doxapram (Gupta and Dundee, 1974; Gawley, Dundee and Jones, 1975; Gawley et al., 1976). Although there was a reduced frequency of cough and spit in our study in patients receiving doxapram (4.5%) as compared with those not receiving doxapram (21.7%), the difference was not statistically significant. Downing and others (1977) found that doxapram only reduced respiratory sequelae in patients not treated with antibiotics. All our patients received prophylactic antibiotic therapy and this may have contributed to the overall result.

Lees and others (1976) have suggested that the effect of doxapram on hypoxaemia may be that of a sparing effect on FRC. FRC measurements would be impossible to interpret in patients in whom portions of lung had been removed, but we may speculate that the impaired lung function in our patients may have included such a large reduction in expiratory reserve volume that this limited the possible beneficial effects of doxapram.

We conclude that, although doxapram may reduce pulmonary complications after operation in fit patients, it has no effect on ventilation or postoperative respiratory complications in patients with lung disease undergoing thoracic surgery.

ACKNOWLEDGEMENTS

We would like to thank A. H. Robins and Co. for supplies of doxapram and the infusion controller, the thoracic surgeons, staff of the respiratory laboratory and nurses at the Brook Hospital for their help and co-operation, Dr C. Penny for reporting the chest x-rays, Drs C. M. T. Gleave and J. G. Bovill for their help and encouragement and Mrs A. van Berkum for secretarial assistance.

REFERENCES

Andersen, R., and Krohg, K. (1976). Postoperative analgesia combined with doxapram. *Anaesthesia*, **31**, 114.

Downing, J. W., Jeal, D. E., Allen, P. J., and Buley, R. (1977). I.v. doxapram hydrochloride and pulmonary complications after lower abdominal surgery. *Br. J. Anaesth.*, **49**, 473.

Gawley, T. H., Dundee, J. W., Gupta, P. K., and Jones, C. J. (1976). Role of doxapram in reducing pulmonary complications after major surgery. *Br. Med. J.*, **1**, 122,

—— —— Jones, C. J. (1975). The role of doxapram in the reduction of pulmonary complications following surgery. *Br. J. Anaesth.*, **47**, 906.

Gupta, P. K., and Dundee, J. W. (1974). Morphine combined with doxapram or naloxone. *Anaesthesia*, **29**, 33.

Kato, H., and Buckley, J. P. (1964). Possible sites of action of the respiratory stimulant effect of doxapram hydrochloride. *J. Pharmacol. Exp. Ther.*, **144**, 260.

Lees, N. W., Howie, H. B., Mellon, A., McKee, A. H., and McDiarmid, A. I. (1976). The influence of doxapram on postoperative pulmonary function in patients undergoing upper abdominal surgery. *Br. J. Anaesth.*, **48**, 1197.

Scott, R. M., Whitwam, J. G., and Chakrabarti, M. K. (1977). Evidence of a role for the peripheral chemoreceptors in the ventilatory response to doxapram in man. *Br. J. Anaesth.*, **49**, 227.

Wang, S. C., and Hirsch, K. (1973). Doxapram. *Lancet*, **2**, 1314.

EFFETS DU DOXAPRAM SUR LES COMPLICATIONS PULMONAIRES POSTOPERATOIRES APRES UNE THORACECTOMIE

RESUME

On a administré par voie intraveineuse à 53 malades une solution à 5% de dextrose et de doxapram à raison de 2 mg ml^{-1}, ou à 5% de dextrose seule après une thoracectomie latérale. On a procédé à des estimations de la Po_2 artérielle, de la Pco_2 et du pH avant l'opération, pendant l'infusion et 7 jours après l'intervention chirurgicale. On a effectué des tests sur la fonction respiratoire avant et

7 jours après l'opération. Il n'y a pas eu de différences importantes dans la $P\text{o}_2$ artérielle, la $P\text{co}_2$ et le pH ou dans les tests de la fonction respiratoire, entre les malades qui avaient reçu du doxapram et ceux auxquels on n'en avait pas administré. Dans cette étude, le doxapram n'a pas affecté la fréquence des complications pulmonaires postopératoires.

WIRKUNGEN VON DOXAPRAM AUF POSTOPERATIVE PULMONARE ERSCHEINUNGEN NACH BRUSTWANDERÖFFNUNG

ZUSAMMENFASSUNG

Eine intravenös verabreichte Losung von 5% Dextrose mit 2 mg ml^{-1} Doxapram, oder von 5% Dextrose allein erhielten 53 Patienten nach einer lateralen Brustwanderoffnung. Schätzungen des arteriellen $P\text{o}_2$, $P\text{co}_2$ und pH wurden vor der Operation, wahrend der Infusion und 7 Tage nach der Operation gemacht. Respiratorische Funktionstests wurden vor und 7 Tage nach der Operation durchgeführt. Zwischen den Patienten, die Doxapram erhielten, und den anderen Patienten gab es keine beachtlichen Unterschiede beim arteriellen $P\text{o}_2$, $P\text{co}_2$ und pH, und auch nicht bei den respiratorischen Funktionstests. In dieser Studie beeinträchtigte Doxapram die Häufigkeit postoperativer pulmonarer Komplikationen nicht.

EFECTOS DEL DOXAPRAM SOBRE COMPLICACIONES PULMONARES A RAIZ DE TORACOTOMIA

SUMARIO

Se administró una solución i.v. de 5% de dextrosa con 2 mg ml^{-1} de doxapram o de 5% de dextrosa sola a 53 pacientes después de una toracotomia lateral. Antes de la operación, se hicieron estimaciones del $P\text{o}_2$, $P\text{co}_2$ y del pH, así como durante la infusión y 7 días después de la operación. Se lleveron a cabo pruebas de la función respiratoria antes de la operación y 7 días después de la misma. No hubo diferencias significativas en el $P\text{o}_2$, $P\text{co}_2$ y pH ni tampoco en las pruebas de la función respiratoria entre los que recibieron doxapram y los que no lo recibieron. En este estudio, el doxapram no afectó la frecuencia de las complicaciones pulmonares postoperatorias.

Br. J. Anaesth. (1980), 52, 85

EVALUATION OF GLYCOPYRROLATE AND ATROPINE AS ADJUNCTS TO REVERSAL OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS IN A "TRUE-TO-LIFE" SITUATION

D. A. COZANITIS, J. W. DUNDEE, J. D. MERRETT, C. J. JONES AND R. K. MIRAKHUR

SUMMARY

Glycopyrrolate, a quaternary ammonium anticholinergic compound, and atropine were evaluated in combination with neostigmine for antagonism of non-depolarizing neuromuscular block. A total of 641 patients were investigated in a "true-to-life" situation. The patients receiving glycopyrrolate with neostigmine had smaller changes in heart rate than those who received atropine. This was particularly apparent in patients with cardiovascular disease.

Glycopyrrolate (glycopyrronium bromide, Robinul) is a potent quaternary ammonium anticholinergic compound. Several studies have demonstrated its efficacy in blocking the muscarinic actions of neostigmine (Klingenmaier, et al., 1972; Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977). All the studies have taken place under carefully controlled conditions and involved relatively small numbers of patients. Although such preliminary studies are absolutely essential, it is conceivable that such investigations may have little relevance to the use of the drug in normal anaesthetic practice. Accordingly, we have evaluated glycopyrrolate in a "true-to-life" situation.

METHODS

Twenty-eight anaesthetists of varying seniority from seven centres in Northern Ireland participated in the study. Each was free to choose any premedication and anaesthetic drug he considered suitable for the patients. All procedures, except open heart and neurosurgery, which involved the use of non-depolarizing neuromuscular blockers were included, and the block was antagonized routinely at the end of the operation.

Neostigmine methyl sulphate 0.05 mg kg^{-1} was given i.v. in combination with either atropine 0.02 mg kg^{-1} or glycopyrrolate 0.01 mg kg^{-1} from coded ampoules using a double-blind technique. Allocation to either drug was random. Heart rate from the radial pulse and arterial pressure obtained by the Riva Rocci method were measured immediately before administration of the mixture and at 1, 2, 3, 4, 5, 7 and 10 min after, and thereafter at 5-min intervals up to the 40th minute. Subsequently, the measurements were made at 15-min intervals until 115 min. At each time, the anaesthetist's subjective assessment of salivation (unacceptably moist, moist, dry) and degree of reversal (incomplete, adequate, complete) were also recorded on simple three-point scales.

If, at any time, the quality of antagonism was judged by the investigator to be inadequate, or if severe muscarinic side-effects occurred, further doses of the mixture, atropine or neostigmine, were administered.

Data were recorded on specially designed computer-compatible forms. Relevant patient information and details of all drugs and the doses used in the periods before, during and after the operation were recorded. If any patient required atropine during the period of observation, the data following the time of administration were excluded.

Student's *t* test was used for parametric analyses and either Fisher's exact test or the chi-squared test for non-parametric data.

RESULTS

The study was carried out over a 6-month period during which satisfactory data were obtained from 641 patients. The relevant details are shown in table I. Apart from the significantly larger proportion of patients with concurrent disease in the glycopyrrolate

---

D. A. COZANITIS,* B.SC.PHARM., M.D., D.T.M.H.; J. W. DUNDEE, M.D., PH.D., F.F.A.R.C.S., M.R.C.P.; R. K. MIRAKHUR, M.D., PH.D., F.F.A.R.C.S.; Department of Anaesthetics, The Queen's University of Belfast, Belfast, Northern Ireland. J. D. MERRETT, PH.D., Department of Medical Statistics, The Queen's University of Belfast. C. J. JONES, B.PHARM., M.P.S., A. H. Robins Co., Redkiln Way, Horsham, W. Sussex.

*Present address: Department of Anaesthesia, University Central Hospital, 00290 Helsinki, 29, Finland.

0007-0912/80/010085-05 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Some details of the patients*

	Atropine group	Glycopyrrolate group
Number of patients	339	302
Mean age (yr ± SEM)	45 ± 0.9	48 ± 0.9
Mean weight (kg ± SEM)	63 ± 0.7	62 ± 0.7
Sex (% male)	31	31
Concurrent disease (%)	41	50
Median duration of anaesthesia (min)	70	70
Type of operation (%)		
General	42	48
Thoracic and vascular	16	15
Gynaecological	39	36
Urological	3	1
ASA status (%)		
1	64	58
2	25	30
3+4	11	12

group ($P < 0.05$), both groups were similar in all other respects. This difference was a result of a significantly greater proportion of patients with cardiac diseases in the glycopyrrolate group (19% compared with 11%, $P < 0.01$).

Thiopentone was used for induction of anaesthesia in 91% of the patients. Of the 71% of patients who received i.v. analgesia during operation, 53% were given fentanyl, while a variety of other narcotics was administered to the remaining patients. All received nitrous oxide and about two-thirds an additional inhalation agent. Of these patients, 87% received halothane.

The premedicant drugs and neuromuscular blockers used in the study are summarized in table II. There was no statistically significant difference between the two groups in respect of the distribution of drugs used before and during operation.

TABLE II. *Premedicant and non-depolarizing neuromuscular blocker used* (%)

	Atropine group	Glycopyrrolate group
Premedicant		
Atropine	49.0	51.0
Hyoscine	1.5	2.3
Morphine	1.2	1.3
Pethidine	49.6	48.5
Benzodiazepines	41.0	43.0
Others	15.3	14.9
Muscle relaxant		
Pancuronium	65.5	71.9
Tubocurarine	9.1	6.6
Gallamine	14.2	11.6
Others	11.2	9.9

In the entire population, following the injection of the atropine-containing mixture, there was a significant increase in heart rate, but within 3 min there was a sustained and significant decrease in heart rate. However, the mixture with glycopyrrolate produced a significant but smaller initial increase in heart rate and the subsequent reduction in heart rate was less than that following atropine. The differences between the two groups were statistically significant at most times up to 40 min following injection of the drugs under study.

Because of the significant differences between the groups of patients with pre-existing heart disease, such as angina pectoris, hypertension, murmurs, myocardial infarction, and because of the importance of heart rate changes in such patients, it was considered necessary to analyse the data from these patients separately. These patients were well matched with regard to physical characteristics, premedication and therapy during operation. Figure 1 summarizes the heart rate results in this sub-group. The differences between the atropine group and the glycopyrrolate group are more marked than those in the patients without heart disease (fig. 2). In the patients with heart disease, the use of neostigmine and atropine was followed by a statistically significant difference between initial and subsequent heart rates, except at the 3rd and 4th min after injection. In contrast, in the glycopyrrolate group a significant difference from initial values was noted only in the first 4 min following injection; no significant slowing of the heart rate was noted at any time. Statistically significant differences were noted between the heart rates of patients treated with atropine and those treated with glycopyrrolate.

In addition to the analysis of heart rate data by parametric methods, the frequency of clinically important bradycardia was studied; this was taken as a heart rate less than 60 beat min^{-1}. In patients with pre-existing heart disease, a significant difference between the groups was noted at the 10th min, 23% in the atropine group and 4% in the glycopyrrolate group ($P < 0.05$) (fig. 3). There was a greater proportion of patients with bradycardia in the atropine group at other times, although the differences were not statistically significant. There was no statistically significant difference in the completeness of antagonism between the groups at any time.

The proportion of patients with a negligible amount of oral secretions following the administration

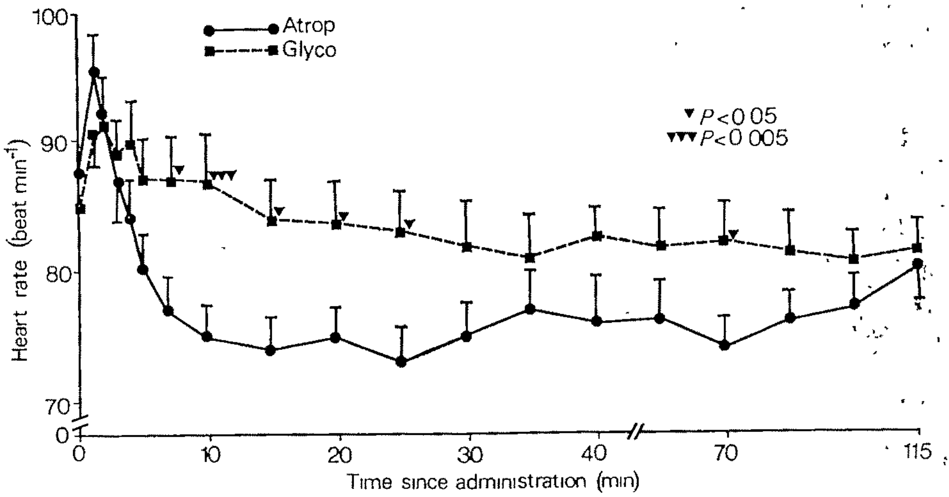


FIG. 1. Mean heart rates at the various time intervals after administration of the reversal mixtures in those patients with pre-existing cardiovascular dysfunction. The statistical differences are between the groups. Vertical bars represent SEM.

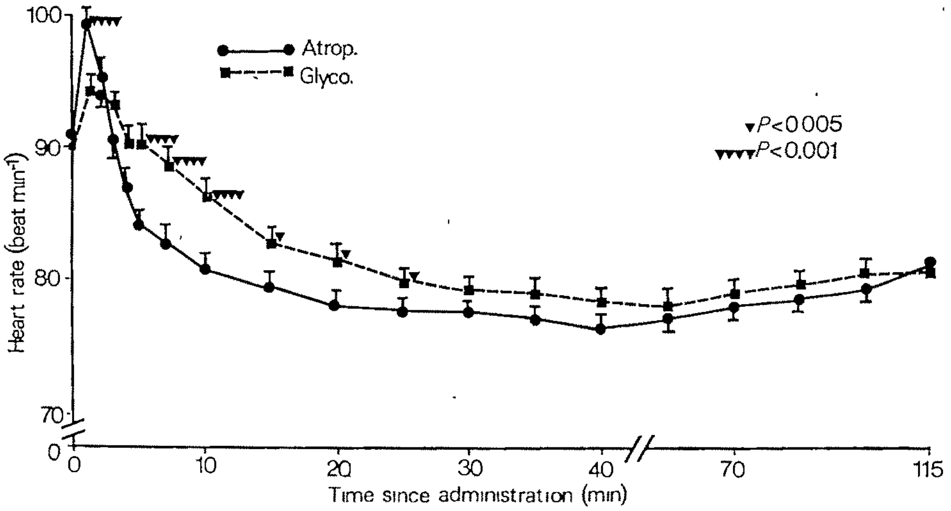


FIG. 2. Mean heart rates at the various time intervals after administration of the reversal mixtures in patients having no cardiovascular dysfunction. The statistical differences are between the groups. Vertical bars represent SEM.

of neostigmine was significantly greater in the first 3 min after injection when glycopyrrolate was used as the anticholinergic ($P < 0.012$ to $P < 0.05$).

Because of inadequate antagonism, a second dose of the neostigmine-containing mixture was required in 4% of all patients.

An additional dose of atropine was given to 51 patients because of bradycardia. The proportion requiring atropine did not differ significantly between those who received atropine (8.9%) and those receiving glycopyrrolate (6.1%). However, in the atropine group, the median time following the administration of the reversal mixture at which supplementary atropine was given was 10 min, whereas in the glycopyrrolate group this occurred at 26 min. A second dose of atropine was given to 21% of the patients with heart disease who had received atropine with neostigmine, compared with 8.6% in

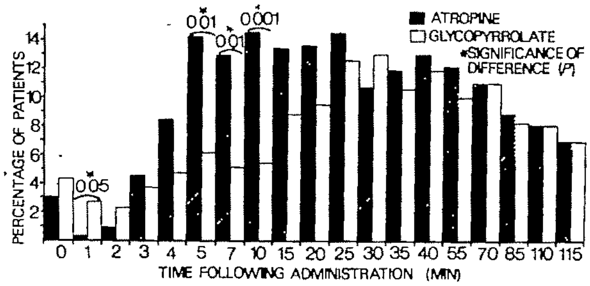


FIG. 3. Percentage of patients showing bradycardia of less than 60 beat min^{-1} at various times after administration of neostigmine with either atropine ator glycopyrlore.

the glycopyrrolate group; these differences were not statistically significant.

Changes in both systolic and diastolic arterial pressure were noted in both groups, but these were well within accepted clinical limits. No statistically significant alterations of heart rate were seen in those patients who had received fentanyl, pancuronium, halothane or gallamine.

DISCUSSION

Antagonism of a myoneural blocking drug with a combination of glycopyrrolate and neostigmine produced a different pattern of cardiovascular response than that produced by atropine and neostigmine. The initial tachycardia which followed injection of the mixtures was less in patients receiving glycopyrrolate, as was the subsequent decrease in heart rate. The overall finding was of a more stable cardiovascular system following reversal using glycopyrrolate. These results are in broad agreement with the findings of other workers (Ramamurthy, Shaker and Winnie, 1972; Klingenmaier et al., 1972; Mirakhur, Dundee and Clarke, 1977; Ostheimer, 1977), although in a group of 20 patients Mirakhur, Dundee and Clarke (1977) failed to demonstrate an initial increase in heart rate following antagonism with neostigmine 2.5 mg and glycopyrrolate 0.5 mg—the same ratio of drugs as that used in the present study. This difference may be explained on the basis of a body weight-related dose of 0.01 mg kg^{-1} in the present study and a smaller mean dose of 0.0076 mg kg^{-1} in the study of Mirakhur, Dundee and Clarke (1977).

It may be argued that the changes in heart rate noted here are not of clinical importance in patients with normal cardiovascular status. However, they may be important in patients with pre-existing heart disease. Our analyses demonstrated that, in such patients, administration of atropine with neostigmine produced wide and sudden changes in heart rate. In contrast, patients in the glycopyrrolate group maintained a more stable heart rate. Thus glycopyrrolate may be preferable to atropine in these subjects.

The quaternary nature of the ammonium group makes glycopyrrolate a compound which is completely ionized; this results in a slower onset of activity. It becomes apparent, therefore, that both neostigmine and glycopyrrolate have similar onset times of activity, thereby reducing the risk of increase in heart rate so often seen when neostigmine is given with atropine.

In those few patients who required an additional anticholinergic agent (atropine) to counteract excessive bradycardia, this was needed much later when glycopyrrolate was used as compared with atropine. This agrees with earlier work which showed that glycopyrrolate has a long duration of anticholinergic action (Wyant and Kao, 1974; Mirakhur, Dundee and Jones, 1978).

In retrospect, we should have recorded the cardiac medication taken by patients. However, the resting heart rate in the cardiac sub-group was not significantly less than in the non-cardiac patients. This suggests that beta-blockers, for example, did not have a marked effect on our results.

The greater proportion of patients with an acceptable degree of oral secretions in the glycopyrrolate group confirms the potent anti-sialogogue activity of this compound (Wyant and Kao, 1974).

In the present study, the dose of neostigmine was 0.05 mg kg^{-1} and that of atropine, 0.02 mg kg^{-1}: a ratio of 2.5 : 1. It is not uncommon to use a fixed dose of neostigmine 2.5 mg and atropine 1.2 mg, a ratio of 2 : 1. Although one might attempt to explain the bradycardia on the basis of insufficient atropine, Mirakhur, Dundee and Clarke (1977) showed a similar response in heart rate when the neostigmine/atropine ratio was 2 : 1.

It is interesting to note that, although there was no control of patient selection, anaesthetic and surgical techniques and immediate postoperative care of our patients, the results from this "true-to-life" study produced data comparable to that from the initial carefully controlled investigations. This type of evaluation of new drugs might be attempted, when possible, to assess better their therapeutic and toxicological spectrum when used under clinical conditions.

It appears that antagonism of the non-depolarizing neuromuscular block using a combination of glycopyrrolate and neostigmine has advantages over the traditional combination of atropine and neostigmine. This advantage might be of particular value to those patients with cardiovascular disease. A more detailed study of such patients is necessary.

ACKNOWLEDGEMENTS

We would like to thank our anaesthetist colleagues for providing the patients and for co-operating in their evaluation. The co-operation of all the nursing staff is gratefully acknowledged, as is the assistance from the Department of Medical Statistics, The Queen's University of Belfast. A. H. Robins Ltd, Horsham, West Sussex, kindly provided the double-blind ampoules and financial assistance.

REFERENCES

Klingenmaier, C. H., Bullard, R., Thompson, D., and Watson, R. (1972). Reversal of neuromuscular blockade with a mixture of neostigmine and glycopyrrolate. *Anesth. Analg.* (*Cleve.*), **51**, 468.

Mirakhur, R. K., Dundee, J. W., and Clarke, R. S. J. (1977). Glycopyrrolate–neostigmine mixture for antagonism of neuromuscular block: comparison with atropine–neostigmine mixture. *Br. J. Anaesth.*, **49**, 825.

—— ——, Jones, C. J. (1978). Evaluation of the anticholinergic actions of glycopyrronium bromide. *Br. J. Clin. Pharmacol.*, **5**, 77.

Ostheimer, G. W. (1977). A comparison of glycopyrrolate and atropine during reversal of nondepolarizing neuromuscular block with neostigmine. *Anesth. Analg.* (*Cleve.*), **56**, 182.

Ramamurthy, S., Shaker, M. H., and Winnie, A. P. (1972). Glycopyrrolate as a substitute for atropine in neostigmine reversal of muscle relaxant drugs. *Can. Anaesth. Soc. J.*, **19**, 399.

Wyant, G. M., and Kao, E. (1974). Glycopyrrolate methobromide. I: Effect of salivary secretion. *Can. Anaesth. Soc. J.*, **21**, 230.

EVALUATION DU GLYCOPYRROLATE ET DE L'ATROPINE EN TANT QU'AUXILIAIRES POUR L'INVERSION DES AGENTS DE BLOCAGE NEUROMUSCULAIRES NON DEPOLARISANTS DANS UNE SITUATION VECUE

RESUME

Le glycopyrrolate, composé quaternaire anticholinergique d'ammonium, et l'atropine ont été évalués en combinaison avec la néostigmine pour assurer l'antagonisme du blocage neuromusculaire non dépolarisant. On a fait des recherches sur 641 malades dans une situation "vécue". Les malades auxquels on avait administré du glycopyrrolate avec la néostigmine ont eu de plus petites variations dans la fréquence cardiaque que ceux auxquels on avait administré de l'atropine. Ceci a été particulièrement évident chez les malades souffrant de maladie cardiovasculaire.

BEWERTUNG VON GLYCOPYRROLAT- UND ATROPIN-ZUTATEN ZUR UMKEHRUNG EINER NICHTDEPOLARISIERENDEN NEUROMUSKULÄREN BLOCKIERUNG IN EINER "LEBENSECHTEN" SITUATION

ZUSAMMENFASSUNG

Glycopyrrolat, eine quarternäre Ammoniumanticholinergische Verbindung, und Atropin wurden im Kombination mit Neostigmin für Aufhebung einer nichtdepolarisierenden neuromuskulären Blockierung untersucht. Insgesamt 641 Patienten wurden in einer "lebensechten" Situation untersucht. Die Patienten, die Glycopyrrolat mit Neostigmin erhielten, wiesen kleinere Änderungen der Herztatigkeit auf als jene, die Atropin erhielten. Dies wurde besonders offenbar bei Patienten, die an Herz-Kreislaufstorungen litten.

EVALUACION DE LOS ADITIVOS DE GLICOPIRROLATO Y ATROPINA PARA LA REVERSION DE LOS AGENTES BLOQUEADORES NEUROMUSCULARES NO-DEPOLARIZANTES EN UNA SITUACION "VIDA REAL"

SUMARIO

Se evaluaron el glicopirrolato, un compuesto cuaternario anticolinérgico de amonio y la atropina en combinación con neoestigmina respecto de su antagonismo con el bloqueo neuromuscular no-depolarizante. Se averiguó a 641 pacientes en total en una situación de "vida real". Los pacientes que recibieron glicopirrolato con neoestigmina registraron alteraciones menores del ritmo cárdiaco que los a quienes se administró atropina. Eso fue más marcado en los pacientes que padecían de enfermedades cardiovasculares.

Br. J. Anaesth. (1980), **52**, 91

I.V. PRACTOLOL DURING MICROLARYNGOSCOPY. EFFECT ON ARTERIAL PRESSURE, HEART RATE, BLOOD GLUCOSE AND LIPOLYSIS

O. WERNER, J. MAGNUSSON, R. FLETCHER, P. NILSSON-EHLE AND O. PAHLM

SUMMARY

Twenty-five patients undergoing microlaryngoscopy were anaesthetized with thiopentone and nitrous oxide with suxamethonium as a muscle relaxant. Thirteen received practolol 0.4 mg kg^{-1} and atropine 1.5 mg i.v. shortly before anaesthesia. During anaesthesia practolol 0.2 mg kg^{-1} was given. Twelve (control) received atropine 0.5 mg before anaesthesia. Practolol reduced the frequency of tachycardia and arrhythmia. The treatment group had a greater reduction in systolic arterial pressure during induction. The hypertensive response to laryngoscopy was not significantly attenuated by practolol. A weak hyperglycaemic response to microlaryngoscopy was not affected, nor was the plasma concentration of glycerol.

I.v. β_1 selective adrenoceptor blockade has been tried to combat the circulatory response to laryngoscopy and tracheal intubation. Although there is a good effect in limiting tachycardia and arrhythmia, conflicting results have been obtained in respect of protection against increases in arterial pressure. Prys-Roberts and others (1973) used practolol (Eraldin, I.C.I.) in hypertensive subjects, and found a significant attenuating effect. Similar results were obtained by Ryhänen and others (1977). Siedlecki (1975) found no effect on the hypertensive response. However, different types of anaesthesia were used in those three studies and the assignment of patients to treatment or control groups was, apparently, not strictly randomized.

Microlaryngoscopy causes a similar but more lasting cardiovascular response (Weigand, 1970). We describe a randomized trial on the cardiovascular effects of i.v. practolol during microlaryngoscopy. To test whether the procedure leads to a metabolic stress response and whether this response can be attenuated by practolol, we measured blood-glucose and plasma glycerol concentrations. The latter is considered to be the most sensitive indicator of adipose tissue lipolysis (Havel, 1965).

PATIENTS AND METHODS

Twenty-five patients undergoing microlaryngoscopy were studied. Those with diabetes, obstructive lung disease, inspiratory difficulties, congestive heart failure, second or third degree A–V block, moderate or severe heart enlargement on chest x-ray were excluded, as were patients receiving digitalis or antihypertensive treatment, including beta-blockers. Informed consent was obtained from the patients.

The patients were fasted from midnight. In the morning, a 12-lead e.c.g. was taken and arterial pressure measured after 10–15 min of rest. A portable e.c.g. recorder (SRA, Sweden) was attached. One lead (modified V_5) was used. The patients were premedicated with morphine and hyoscine i.m. according to age (table I). On arrival at the operating theatre, the patient lay recumbent for 10–15 min, after which blood was sampled through a plastic i.v. cannula. E.c.g. leads were attached for oscilloscope monitoring. Allocation to practolol or saline (control) treatment was random. The anaesthetist, but not the person measuring arterial pressure, knew the nature of the treatment given. Immediately before injections systolic arterial pressure was measured by radial artery palpation. The same cuff (width 12 cm) and anaeroid manometer were used for all patients. The manometer had been checked against a mercury manometer and been found to be correct within 4 mm Hg in the range 0–260 mm Hg. All patients were first given atropine sulphate 0.5 mg i.v. so that the heart rate response would not reveal which drugs were given subsequently. Thereafter, either saline (controls) or atropine 1.0 mg (treatment group) was given. Practolol 0.4 mg kg^{-1} or saline was administered during 4 min, starting 1 min after the injection of atropine. Two minutes later, thiopentone was

---

O. WERNER, M.D.; J. MAGNUSSON, M.D.; R. FLETCHER, F.F.A.R.C.S.; Department of Anaesthesia. P. NILSSON-EHLE, M.D., Department of Clinical Chemistry. O. PAHLM, M.D., Department of Clinical Physiology. University Hospital of Lund, S-221 85 Lund, Sweden.

0007-0912/80/010091-06 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Some comparisons of the two groups. Values are given as mean ± 1 SD (when applicable). ML = microlaryngoscopy*

	Treatment	Control
Males/females	13/0	11/1
Age (yr)	58 ± 12	50 ± 16
Weight (kg)	77 ± 12	78 ± 17
Resting arterial pressure (mm Hg)		
Systolic	139 ± 16	135 ± 24
Diastolic	77 ± 9	80 ± 11
Heart rate at rest (beat min^{-1})	66 ± 9	59 ± 10
Premedication		
Morphine (mg)	8.4 ± 3.1	9.3 ± 3.8*
Hyoscine (mg)	0.34 ± 0.12	0.37 ± 0.12
Induction		
Thiopentone (mg kg^{-1})	4.2 ± 0.4	4.7 ± 0.6
Suxamethonium (mg kg^{-1})	1.1 ± 0.2	1.1 ± 0.2
Time intervals (min)		
Premedication–anaesthesia	75 ± 34	78 ± 25
Induction–intubation	2.8 ± 0.6	2.9 ± 0.6
Intubation–start of ML	5 ± 2	5 ± 2
Start–end of ML	14 ± 10	14 ± 7
End of ML–extubation	5 ± 4	6 ± 4
Subjects receiving fentanyl	3	4
Mean dose of fentanyl in these subjects (mg)	0.12	0.15

* One subject received diazepam 5 mg i.m. instead.

injected over approximately 1 min, followed by suxamethonium. The lungs were ventilated with 5–10 breaths of oxygen, after which the trachea was intubated with the aid of a Macintosh laryngoscope. The tube (cuffed Portex 6.5) was lubricated with tetracaine gel; otherwise, no topical anaesthesia was given. Subsequently, the lungs were ventilated manually with nitrous oxide 70% in oxygen. A suxamethonium infusion (2 mg ml^{-1} in Ringer solution) was started when the patient showed signs of recovering from the initial paralysis. During the induction of anaesthesia systolic arterial pressure was measured and recorded every 30–45 s. Thereafter arterial pressure was measured every minute throughout the procedure. No fentanyl was given before or during induction. During microlaryngoscopy fentanyl 0.1 mg was given if the systolic pressure was 200 mm Hg or greater, for at least 2 min. A further 0.1 mg was given if arterial pressure was greater than 225 mm Hg. Practolol 0.2 mg kg^{-1} or saline was given slowly between 12 and 14 min after the end of the first injection, about 10–12 min after the start of anaesthesia. Blood was sampled 20 min after the start of anaesthesia. The arterial pressure measurements continued at 1-min intervals until 2 min after extubation.

Analyses. Electrocardiograph tapes were replayed on a computer system (Pahlm et al., 1978). Significant events, such as injections, were identified with a marker pulse. An e.c.g. record covering the whole procedure was written on paper (25 mm s^{-1}). Arrhythmia was evaluated from the e.c.g. record by an observer who was unaware of the treatment. Heart rate was measured from e.c.g. every 20 s beginning 1 min before the injection of atropine. The blood samples were immediately placed in ice. Samples for analysis of blood-glucose were drawn in tubes containing sodium fluoride and analysed within 6 h by an enzymatic–colorimetric method (Marks, 1959). Blood samples for glycerol analysis were drawn in tubes containing EDTA. Plasma was separated by centrifugation immediately after operation, and stored at −20 °C. Glycerol concentrations were measured by an enzymatic-fluorimetric method (Laurell and Tibbling, 1966).

Statistics. The Mann–Whitney (two-sided) rank sum test for unpaired data was used for between-group comparisons. The Wilcoxon (two-sided) rank sum test for paired data was used for within-group comparisons. Probability values <0.05 were considered to indicate statistical significance.

RESULTS

There were no notable differences between the groups in respect of resting arterial pressure, weight, premedication, anaesthetic drugs given and duration of the procedure, except that the controls received slightly more thiopentone (table I).

Systolic arterial pressure. Mean arterial pressure at rest immediately before injection of atropine was similar in the two groups. Compared with the initial pressure, no significant change in systolic arterial pressure occurred during or after the first injection of practolol or saline in either group. Minimum arterial pressure during induction was less in the practolol group ($P<0.05$) (fig. 1). Maximum arterial pressure within 2 min after laryngoscopy and intubation was greatest in the control group. However, a large increase in arterial pressure occurred in the treatment group, so that the difference between groups was not statistically significant. Usually the arterial pressure decreased during the few minutes before microlaryngoscopy, but when microlaryngoscopy began, arterial pressure increased, remaining increased in both groups during the rest of the procedure, and also after repeated injection of saline or practolol 0.2 mg kg^{-1}.

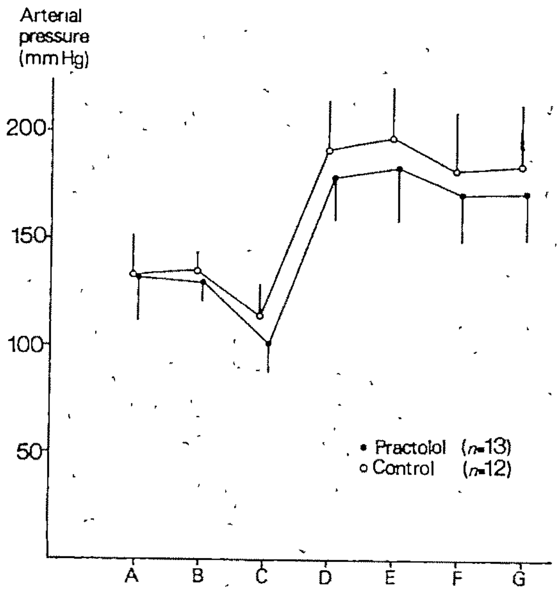


FIG. 1. Systolic arterial pressure before and during microlaryngoscopy (group mean and 1 SD). A = Immediately before injections; B = 1 min after injection of atropine and practolol (saline). Patient still awake; C = smallest value recorded during induction (this always occurred before intubation); D = greatest value within 2 min after laryngoscopy and intubation; E = greatest value during microlaryngoscopy; F = mean value during microlaryngoscopy; G = 2 min after repeated injection of practolol 0.2 mg kg^{-1} or saline. SD in panel A was calculated directly from the recorded values, while panels B–G show the standard deviation of the change in relation to A.

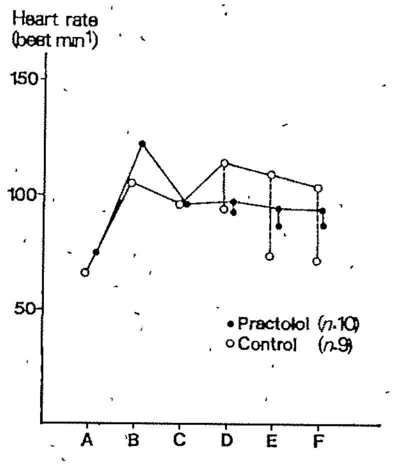


FIG. 2. Heart rate (group means): A = before injections; B = maximum after atropine; C = 1 min after practolol; D = maximum/minimum during induction; E = maximum/minimum during diagnostic laryngoscopy; F = maximum/minimum during awakening.

Heart rate. The tape recording failed for various technical reasons in three subjects of each group. In the remaining subjects, no significant differences between groups were found immediately before atropine (fig. 2). Compared with the initial heart rate, the increase after atropine was greater in the treatment group (who received 1.5 mg) than in the other group (0.5 mg), although the difference was not significant. The heart rate decreased more after practolol than after saline, so that heart rates were again nearly equal 1 min after practolol or saline injection. Induction of anaesthesia and intubation caused very little response in the treatment group, while the maximum heart rate in the other group was significantly greater in relation to the initial heart rate ($P < 0.01$). The controls also had significantly greater maximum heart rates during microlaryngoscopy ($P < 0.01$) and during awakening and extubation ($P < 0.05$) and there was greater variation in heart rate during the procedure (fig. 2).

Arrhythmia. Among 10 e.c.g. tapes from the practolol group, one showed a total of three ventricular extrasystoles during and shortly after injection of practolol. Otherwise, no arrhythmia was seen except sinus tachycardia in some cases.

Among nine tapes from the controls, three showed junctional rhythm during intubation, while other disturbances of rhythm were observed shortly after atropine in two patients (marked sinus arrhythmia and ventricular extrasystoles respectively). One patient already had ventricular extrasystoles before atropine. These persisted and increased in number during microlaryngoscopy.

Blood-glucose and plasma glycerol. Blood-glucose increased slightly during anaesthesia in both groups (table II). The increase was significant only in the practolol group ($P < 0.05$). The difference in blood-glucose between the groups was not significant. The initial mean plasma glycerol concentrations were slightly greater than the upper reference limit (100 μmol $litre^{-1}$). In the control group, plasma

TABLE II. *Mean blood-glucose and plasma glycerol concentrations before and during anaesthesia. Numbers within parentheses show SD of the initial value/SD of the change*

	Treatment		Control	
	Before	During	Before	During
Blood-glucose (mmol $litre^{-1}$)	5.6 (0.7)	6.0 (0.7)	5.5 (1.3)	5.7 (0.7)
Plasma glycerol (μmol $litre^{-1}$)	122 (46)	114 (48)	144 (63)	151 (49)

glycerol concentrations increased slightly during microlaryngoscopy; in the practolol group there was a small decrease in mean glycerol concentration. The difference in response between the two groups, was not statistically significant (table II).

DISCUSSION

Heart rate and contractility are stimulated via beta adrenoceptors, mainly β_1 (Carlsson et al., 1977). The degree of blockade of cardiac beta adrenoceptors appears to be closely related to the plasma concentration of the beta blocker (Vaughan Williams et al., 1975). The relation between plasma concentration and antihypertensive effect is less direct. Thus, a single dose of beta blocker does not greatly reduce arterial pressure (Tarazi and Dustan, 1972). The full effect is seen only after a few hours or days of treatment (Conway and Amery, 1975). Likewise, a single dose suppresses the tachycardia associated with mental stress, but has little effect on the hypertensive response (Nyberg, Graham and Stokes, 1977). The same applies to the effects of beta blockers on the circulatory response to isometric exercise (Sangvik et al., 1975) and to the effects during direct stimulation of the defense–alarm area of the dog brain (Åblad et al., 1975). Thus, except for dynamic exercise, short-term administration of beta blockers does not greatly attenuate the hypertensive response associated with many types of stress. However, they do reduce heart rate.

Since acute administration is rather ineffective in the awake subject, it is far from evident that beta blockers are effective antihypertensive agents during anaesthesia. One thing is to be expected, namely interaction between the beta blocker, external stimuli and the anaesthetic, which always exerts its own effects on the cardiovascular system. The present findings support this concept. The greater decrease in systolic arterial pressure during induction in the treatment group may be explained by such interaction. Thiopentone seems to cause a pooling of blood in the systemic capacitance vessels, by depression of medullary centres. This reduces cardiac output and, usually, arterial pressure (Conway and Ellis, 1969). An additional effect of practolol, further reducing cardiac output and arterial pressure, is likely. During laryngoscopy and intubation, the central depressant action of thiopentone is strongly counteracted. This may explain why practolol did not significantly attenuate the hypertensive response —paralleling the lack of effect of beta blockers in awake subjects under stress.

Carruthers and others (1974) showed a rapid reduction in plasma concentration of practolol after i.v. injection. This is not an explanation for the lack of significant antihypertensive effect during intubation or microlaryngoscopy. In both cases, plasma concentrations were obviously great enough to inhibit tachycardia. Also, the arterial pressure was not much less among those treated than among those not treated 2 min after a repeated injection of practolol (saline).

We followed the recommendation of Prys-Roberts and others (1973), to give a generous dose of atropine before practolol in order to avoid bradycardia. We do not believe that practolol without atropine would have been more effective against the hypertensive response, although heart rates would, of course, have been slower. Our belief is based on the studies cited in the first paragraph of this discussion. As mentioned, acute beta blockade (without atropine) reduced stress-induced tachycardia, but had little effect on the hypertensive response.

The present results agree with those of Siedlecki (1975), who used the same type of induction and did not find any attenuation by practolol of the arterial pressure response to intubation. Superficially, the results contradict those of Prys-Roberts and others (1973), who studied hypertensive subjects intubated under halothane–nitrous oxide anaesthesia, and those of Ryhänen and others (1977), who used thiopentone combined with halothane–nitrous oxide in a mixed group of normo- and hypertensive patients. They found that i.v. practolol did reduce the arterial pressure response to laryngoscopy and intubation. We believe that the discrepancy may be explained by the type of anaesthesia used. Thus, halothane has potent cardiovascular effects, particularly as a myocardial depressant (Prys-Roberts et al., 1972). Practolol may have potentiated the effect of halothane. This explanation may seem difficult to reconcile with the findings by Slogoff and others (1977) who found, in experiments on dogs under isoprenaline challenge, that halothane does not potentiate the haemodynamic effects of propranolol. Also propranolol actually *increased* the mean aortic pressure in these experiments, although cardiac output decreased. However, the beta stimulation by isoprenaline is probably not analogous to the sympathetic stimulation caused by laryngoscopy. Furthermore, propranolol is non-selective and therefore counteracts the systemic vasodilator effects of β_2 stimulation.

Our conclusions are that beta blockade, instituted shortly before or during anaesthesia, does not effectively counteract the hypertensive response to laryngoscopy, unless other agents are also given which are potentiated by the beta blocker. Deep general anaesthesia (King et al., 1951) or thorough topical analgesia (Stoelting, 1977) would seem to give more predictable effects. In order to reduce the hypertensive response to microlaryngoscopy, we prefer to complement thiopentone–nitrous oxide anaesthesia with fentanyl 0.2–0.5 mg and to give naloxone after the procedure, if necessary. This seems to reduce the arterial pressure response. At the time of these studies, however, the practice at our hospital was to use fentanyl sparingly and it was used about equally often in both groups (table I). The comparison between the groups ought not to have been affected, therefore.

In contrast to its effect on hypertension, a single dose of beta blocker is certainly effective against tachycardia during anaesthesia and operation. This was the case in the present study and several previous ones (Ryder, Charlton and Gorman, 1973). The effect on stress-induced arrhythmia is also striking (Katz and Bigger, 1970). However, for the latter purpose, much smaller doses are needed than those employed in the present study.

Non-selective beta blockade has been shown to attenuate the hyperglycaemic and lipolytic response to stress (Taggart and Carruthers, 1972). In the present study, a weak hyperglycaemic response to microlaryngoscopy was obtained, which was not affected by practolol. Perhaps surprisingly, the procedure had no significant effect on plasma glycerol concentrations. Also, there was no significant difference in lipolytic response between the groups. The last result is consistent with the observations of Gibbons and others (1976), who found that practolol does not affect the basal level of lipolysis, but has a weak inhibitory effect on isoprenaline-induced lipolysis.

ACKNOWLEDGEMENT

We thank Drs N. Dahlgren and K. Messeter for showing us their data on pretreatment with fentanyl before intubation.

REFERENCES

Åblad, B., Carlsson, E., Dahlöf, C., and Ek, L. (1975). Some aspects on the pharmacology of adrenergic β-receptor blockers; in *Pathophysiology and Management of Arterial Hypertension* (eds G. Berglund, L. Hansson and L. Werko), p. 152. Molndal, Sweden: A. Lindgren & Söner.

Carlsson, E., Dahlöff, C.-G., Hedberg, A., Persson, H., and Tångstrand, B. (1977). Differentiation of cardiac chronotropic and inotropic effects of β-adrenoceptor agonists. *Naunyn Schmiedebergs Arch. Pharmacol.*, **300**, 101.

Carruthers, S. G., Kelly, J. G., McDevitt, D. G., and Shanks, R. G. (1974). Blood levels of practolol after oral and parenteral administration and their relationship to exercise heart rate. *Clin. Pharmacol. Ther.*, **15**, 497.

Conway, C. M., and Ellis, D. B. (1969). The haemodynamic effects of short-acting barbiturates. *Br. J. Anaesth.*, **41**, 534.

Conway, J., and Amery, A. (1975). The antihypertensive effect of propranolol and other β-adrenoceptor antagonists; in *Central Action of Drugs in the Regulation of Blood Pressure* (eds D. Davies and J. Reid), p. 277. London: Pitman Medical Publishing Co. Ltd.

Gibbons, D. O., Lant, A. F., Ashford, A., Collins, R. F., and Pinder, S. (1976). Comparative effects of acebutolol and practolol on the lipolytic response to isoprenaline. *Br. J. Clin. Pharmacol.*, **3**, 177.

Havel, R. J. (1965). Some influences of the sympathetic nervous system and insulin on the mobilization of fat from adipose tissue: studies of the turnover rates of free fatty acid and glycerol. *Ann. N.Y. Acad. Sci.*, **131**, 91.

Katz, R. L., and Bigger, J. T. (1970). Cardiac arrhythmias during anesthesia and operation. *Anesthesiology*, **33**, 193.

King, B. D., Harris, L. C., Greifenstein, F. E., Elder, J. D., and Dripps, R. D. (1951). Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. *Anesthesiology*, **12**, 556.

Laurell, S., and Tibbling, G. (1966). An enzymatic–fluorimetric micromethod for the determination of glycerol. *Clin. Chim. Acta*, **13**, 317.

Marks, V. (1959). An improved glucose oxidase method for determining blood, c.s.f. and urine glucose levels. *Clin. Chim. Acta*, **4**, 395.

Nyberg, G., Graham, R. M., and Stokes, G. S. (1977). The effect of mental arithmetic in normotensive and hypertensive subjects, and its modification by β-adrenergic receptor blockade. *Br. J. Clin. Pharmacol.*, **4**, 469.

Pahlm, O., Börjesson, P. O., Johansson, K., Jonson, B., Petersson, K., Sörnmo, L., and Werner, O. (1978). Efficient data compression and arrhythmia detection for long-term e.c.g.s; in *Proc. "Computers in Cardiology 1978"*. IEEE, Inc.

Prys-Roberts, C., Foex, P., Biro, G. P., and Roberts, J. G. (1973). Studies of anaesthesia in relation to hypertension. V: Adrenergic beta-receptor blockade. *Br. J. Anaesth*, **45**, 671.

—— Gersh, B. J., Baker, A. B., and Reuben, S. R. (1972). The effects of halothane on the interactions between myocardial contractility, aortic impedance, and left ventricular performance. I: Theoretical considerations and results. *Br. J. Anaesth.*, **44**, 634.

Ryder, W., Charlton, J. E., and Gorman, P. B. W. (1973). Oral atropine and practolol premedication in dental anaesthesia. *Br. J. Anaesth.*, **45**, 745.

Ryhänen, P., Saarela, E., Saukkonen, J., and Hollmén, A. (1977). Circulatory responses to laryngoscopy and endotracheal intubation in patients with and without cardiovascular disease. Effect of prophylactic practolol. *Ann. Chir. Gynaecol.*, **66**, 294.

Sangvik, K., Stokkeland, M., Lindseth-Ditlefsen, E.-M., and Nyberg, G. (1975). Circulation reaction at rest and during isometric and dynamic exercise in hypertensive patients: influence of different adrenergic beta-adrenoceptor antagonists. *Pharmatherapeutica*. **1**, 71.

Siedlecki, J. (1975). Disturbances in the function of cardiovascular system in patients following endotracheal intubation and attempts of their prevention by pharmacological blockade of sympathetic system. *Anaesth. Resus. Inten. Ther.*, **3**, 107.

Slogoff, S., Keats, A. S., Hibbs, C. W., Edmonds, C. H., and Bragg, D. A. (1977). Failure of general anesthesia to potentiate propranolol activity. *Anesthesiology*, **47**, 504.

Stoelting, R. K. (1977). Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology*, **47**, 381.

Taggart, P., and Carruthers, M. (1972). Suppression by oxprenolol of adrenergic response to stress. *Lancet*, **2**, 256.

Tarazi, R. C., and Dustan, H. P. (1972). Beta adrenergic blockade in hypertension. Practical and theoretical implications of long-term hemodynamic variations. *Am. J. Cardiol.*, **29**, 633.

Vaughan Williams, E. M., Raine, A. E. G., Cabrera, A. A., and Whyte, J. M. (1975). The effects of prolonged β-adrenoceptor blockade on heart weight and cardiac intracellular potentials in rabbits. *Cardiovasc. Res.*, **9**, 579.

Weigand, H. (1970). Über die Narkose bei der Mikrolaryngoskopie und endolaryngealen Mikrochirurgie. II: Das reflektorische Kreislaufverhalten und seine Beeinflussung durch Oberflächenanaesthetica. *Anaesthesist*, **19**, 131.

INJECTION INTRA-VEINEUSE DE PRACTOLOL PENDANT UNE MICROLARYNGOSCOPIE. EFFET SUR LA PRESSION ARTERIELLE, LA FREQUENCE CARDIAQUE, LA GLUCOSE DU SANG ET LA LIPOLYSE

RESUME

Vingt-cinq patients soumis à une microlaryngoscopie ont été anesthésiés au thiopentone et au protoxyde d'azote, auxquels on a ajouté un agent de relaxation des muscles: le Suxaméthonium. Treize patients ont reçu du practolol à raison de 0,4 mg kg^{-1} et de l'atropine à raison de 1,5 mg peu avant l'anesthésie. Pendant l'anesthésie, on leur a administré du practolol à raison de 0,2 mg kg^{-1}. Douze témoins ont reçu 0,5 mg d'atropine avant l'anesthésie. Le practolol a réduit la fréquence de la tachycardie et de l'arythmie. La pression artérielle systolique a été considérablement réduite pendant l'induction chez le groupe soumis au traitement. Le practolol n'a pas atténué de façon significative la réaction hypertensive à la laryngoscopie. Une faible hyperglycémie due à la microlaryngoscopie n'a pas été affectée et il en a été de même pour la concentration de glycérol dans le plasma.

PRACTOLOL INTRAVENÖS WÄHREND MIKROLARYNGOSKOPIE. AUSWIRKUNG AUF ARTERIELLEN DRUCK, PULSZAHL, BLUTZUCKER UND LIPOLYSE

ZUSAMMENFASSUNG

Funfundzwanzig Patienten wurden für Mikrolaryngoskopie mit Thiopenton und mit Stickoxyd mit Suxamethonium als Muskelentspannungsmittel narkotisiert. Dreizehn davon erhielten kurz vor der Narkose 0,4 mg kg^{-1} Practolol und intravenös 1,5 mg Atropin. Wahrend der Narkose wurden 0,2 mg kg^{-1} Practolol verabreicht. Zwölf Kontrollpatienten erhielten vor der Narkose 0,5 mg Atropin. Durch Practolol wurde die Häufigkeit von Tachykardie und Arrhytmie verringert. Die Behandlungsgruppe zeigte eine grossere Verringerung des systolischen arteriellen Druckes während Narkoseeinleitung. Die hypertensive Reaktion auf Laryngoskopie wurde durch Practolol nicht wesentlich erhoht. Eine schwache Hyperglykämische Reaktion auf Mikrolaryngoskopie wurde nicht beeinträchtigt, auch nicht die Plasmakonzentration von Glyzerol.

PRACTOLOL I.V. DURANTE MICROLARINGOSCOPIA. EFECTO SOBRE LA PRESION ARTERIAL, EL RITMO CARDIACO, LA GLUCOSA SANGUINEA Y LA LIPOLISIS

SUMARIO

A 25 pacientes sometidos a microlaringoscopia, se les administró tiopentona y óxido nitroso junto con suxametonio como relajante muscular. Trece recibieron 0,4 mg kg^{-1} de practolol y 1,5 mg de atropina i.v. poco antes de la anestesia. Se administró 0,2 mg kg^{-1} de practolol durante la anestesia. Doce (controles) recibieron 0,5 mg de atropina antes de la anestesia. El practolol redujo la frecuencia de la taquicardia y de la arritmia. El grupo tratado experimentó una mayor reducción de la presión arterial sistólica durante la inducción. El practolol no atenuó significativamente la respuesta hipertensiva a la laringoscopia. No hubo efecto en la respuesta hiperglicémica débil a la microlaringoscopia ni tampoco en la concentración de glicerol en el plasma.

Br. J. Anaesth. (1980), **52**, 97

ACCURACY OF NEW GAS FLOWMETERS

J. WAABEN, M. M. BRINKLØV AND D. B. STOKKE

SUMMARY

The accuracy of five new oxygen and nitrous oxide flowmeter units was investigated using the bubble meter method. The results were compared with those previously found in flowmeters withdrawn from clinical use. New oxygen flowmeters demonstrated less inaccuracies than old flowmeters. No differences were found between the nitrous oxide flowmeters. Unacceptable errors were demonstrated at oxygen presettings less than 1 litre min^{-1}, suggesting the grading within this range to be of no value. Marked deviations which exceeded the limits stated by the manufacturer could still be shown at presettings greater than 1 litre min^{-1}. If an exact $F_{I_{O_2}}$ is required, continuous monitoring with a high accuracy oxygen analyser is essential, even using new flowmeters.

Recent studies have shown that the inaccuracy of anaesthetic gas flowmeters withdrawn from clinical practice is considerable (Sadove et al., 1976; Waaben, Stokke and Brinkløv, 1978). Macintosh, Mushin and Epstein (1958) stated that the initial accuracy of flowmeters is approximately ±2%. For Rotameter flowmeters the manufacturer declares a probable error. To the customers the accuracy is affirmed to be ±(5% indicated flow (IF)+0.5% full scale reading (FSR)). In practice, the tubes are inspected with the aid of high accuracy Master flowmeters using series calibration, and the inspection tolerances applied by this method are ±0.5×(5% IF+0.5% FSR). Although unacceptable for research purposes, ±5% IF appears to be adequate for clinical use (Waaben, Stokke and Brinkløv, 1978).

In the present investigation the accuracy of new flowmeter units was checked and the deviations were compared with those obtained previously with old flowmeter units using similar flow rates.

METHODS

Five new flowmeter units (fig. 1) were calibrated using the bubble meter method (Purnell, 1963; Levy, 1964) for which a random error within ±1.8% had been calculated (Waaben, Stokke and Brinkløv, 1978). With the bobbin of the flowmeters adjusted by eye and reset between measurements, the mean of three measurements was used for the calculation of flow rates. Following correction for water vapour pressure, the calculated flows were corrected to 22 °C and 760 mm Hg by applying the formula for turbulent flows. Finally, the results were transformed to per cent deviation from preset flow rates.

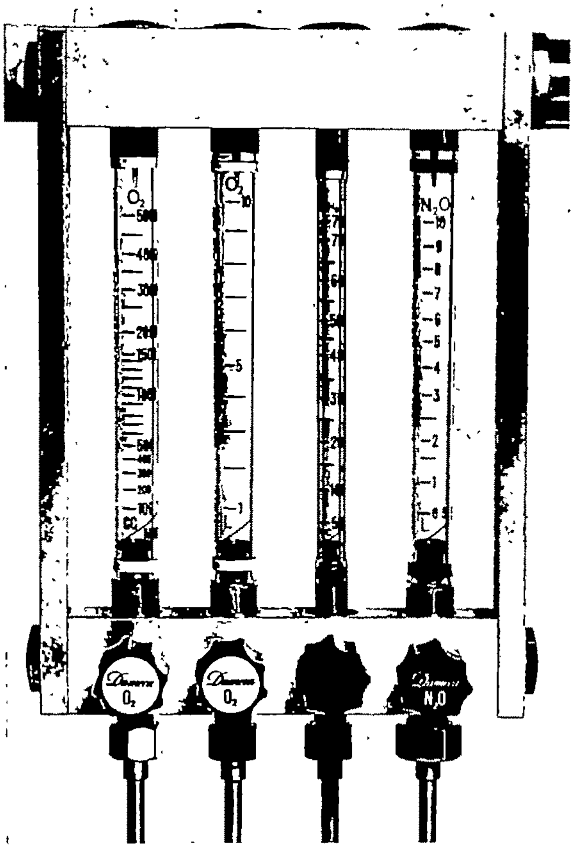


FIG. 1. A new flowmeter unit of the type investigated.

J. WAABEN, M.D.; M. M. BRINKLØV, M.D.; D. B. STOKKE, M.D.; Department of Anaesthesia, Odense University Hospital, DK-5000 Odense C, Denmark.

0007–0912/80/010097–04 $01.00

© Macmillan Journals Ltd 1980

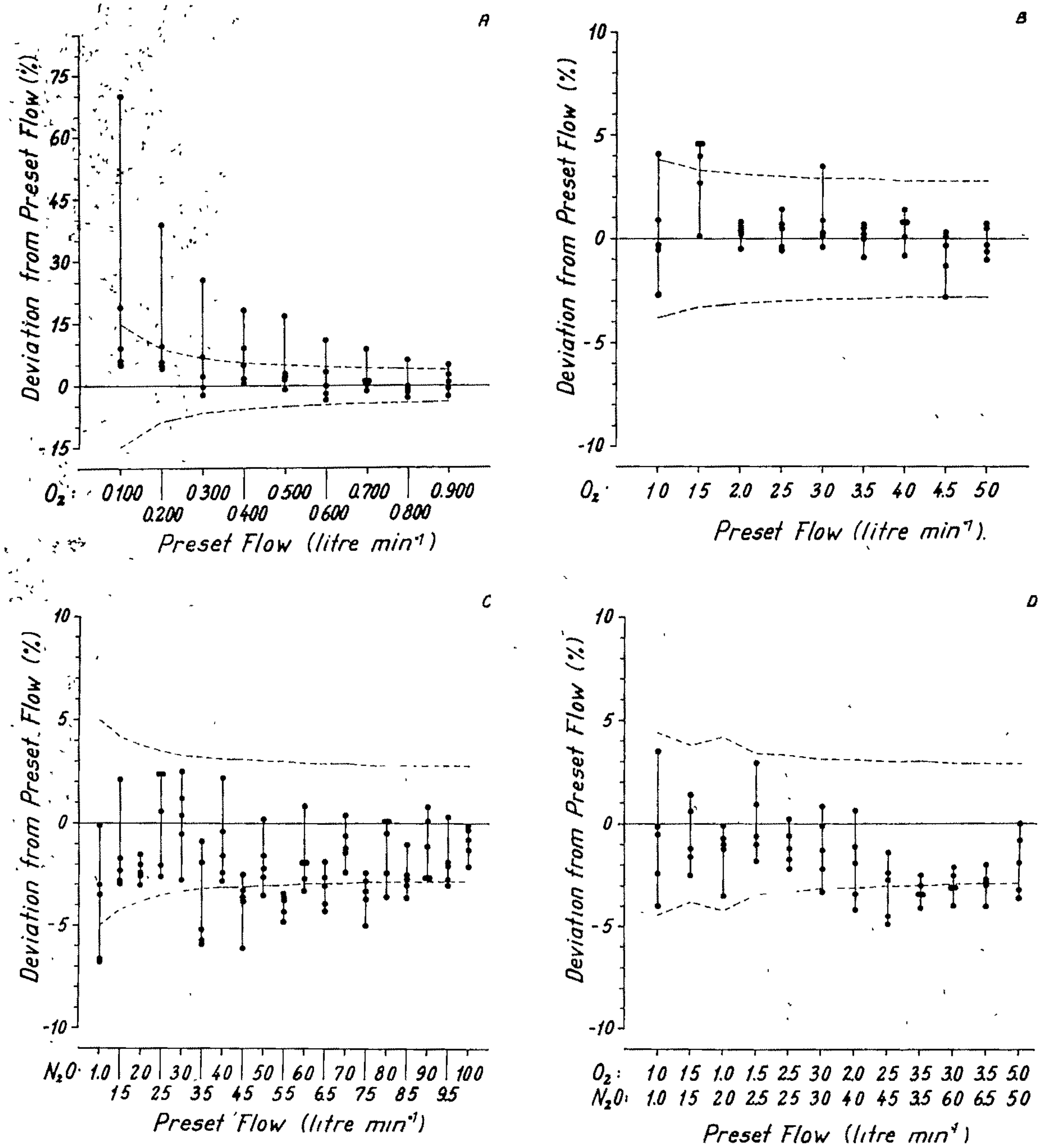


FIG. 2. Deviations from presettings of oxygen, nitrous oxide and mixed flows delivered from five entirely new flowmeter units. Each point represents the mean of three measurements. The dotted lines indicate ±0.5 × (5% indicated flow +0.5% full scale reading).

Non-parametric tests were used in statistical analysis and the level of significance was taken to be 0.01.

For different indicated flow rates the interdependence of the medians of deviations and the indicated flow rates, and of the ranges of deviations and the indicated flow rates was assessed by calculation of Spearman's rank correlation coefficient r_S.

Applying the Wilcoxon test for two samples, the deviations of flows with the bobbin opposite and between the graduation marks of the flowmeters were compared.

Finally, using the chi-square test, comparisons were made between corresponding indicated flow rates delivered from the new flowmeters and from flowmeters withdrawn from clinical use (Waaben, Stokke and Brinkløv, 1978) with regard to the number of observations exceeding ±5% IF and $\pm 0.5 \times (5\% \text{ IF} + 0.5\% \text{ FSR})$ respectively.

RESULTS

The calibration results for the new flowmeters are presented in figures 2A–D, showing the observed deviations at different presettings of gases or gas mixtures.

The most pronounced deviations could be demonstrated at oxygen presettings of less than 1 litre min^{-1} (fig. 2A), the range of the deviations and the median of the deviations being inversely correlated with the preset flow rate ($r_S = -0.98$; $P < 0.001$ and $r_S = -0.87$; $P < 0.01$ respectively).

At presettings greater than 1 litre min^{-1} (fig. 2B–D) the deviations were appreciably reduced, although still marked. With one exception, no correlation was shown between the presettings and the deviations, irrespective of the gas or gas mixture delivered. An inverse correlation was found between the median of the deviations and the preset flow rate of combined flows (fig. 2D) ($r_S = -0.83$; $P < 0.01$).

There was no significant difference between the deviations of the flows obtained with the bobbin opposite and between the graduation marks of the flowmeters, irrespective of the range of presettings and the gas or gas mixture delivered.

Table I shows the results of the comparisons between new and old flowmeters with regard to the number of observations exceeding the calibration limits defined above. For the oxygen flowmeters a highly significant difference in favour of the new flowmeters could be demonstrated, while no differences were found for the nitrous oxide flowmeters or for the combined flows.

DISCUSSION

The extensive deviations demonstrated at oxygen presettings of less than 1 litre min^{-1} indicate that the grading within this range is of no value even for new flowmeters.

At preset flow rates greater than 1 litre min^{-1} many observations exceeded $\pm 0.5 \times (5\% \text{ IF} + 0.5\% \text{ FSR})$ and it appears that even new flowmeters are not within the standard inspection tolerance applied by the manufacturer.

No observation exceeded the range ±5% IF at oxygen presettings greater than 1 litre min^{-1} and at combined flow settings in the range 2–10 litre min^{-1}. However, the accuracy at nitrous oxide presettings in the range 1–10 litre min^{-1} was not quite sufficient, as a few observations exceeded these limits.

TABLE I. *Per cent of observations exceeding the calibration limits for new and old flowmeters with different preset flows of oxygen, nitrous oxide or a mixture of these.* (*IF = indicated flow; FSR = full scale reading*). * *Significant*

Gas and flowrate	Calibration limits	Per cent of observations exceeding the calibration limits: New flowmeters	Old flowmeters	Probability (χ^2 test)
Oxygen	±5% IF	35.5	71.9	<0.0005*
100–900 ml min^{-1}	±0.5 (5% IF+0.5% FSR)	28.9	71.1	<0.0005*
Oxygen	±5% IF	0.0	12.6	<0.01*
1000–5000 ml min^{-1}	±0.5 (5% IF+0.5% FSR)	11.1	37.8	<0.001*
Nitrous oxide	±5% IF	6.3	6.7	>0.80
1000–10 000 ml min^{-1}	±0.5 (5% IF+0.5% FSR)	26.3	21.3	>0.30
Oxygen + nitrous oxide	±5% IF	0.0	6.7	>0.025
2000–10 000 ml min^{-1}	±0.5 (5% IF+0.5% FSR)	23.3	21.7	>0.70

It is surprising that only the new oxygen flowmeters seemed to be superior to the old ones, while no differences were found for the nitrous oxide flowmeters. It appears that the production of initially accurate oxygen flowmeters is easier to accomplish, perhaps because of the smaller range of FSR. The decrease in their accuracy after prolonged use could be a result of the oxygen flowmeters being more sensitive and subjected to more wear than the nitrous oxide flowmeters. The equal inaccuracy found for new and old flowmeters at combined flows could be a reflection of the lack of difference between the new and old nitrous oxide flowmeters.

It is in accordance with the findings for old flowmeters (Waaben, Stokke and Brinkløv, 1978) that no difference could be demonstrated between the flows obtained with the bobbin opposite and between the graduation marks.

In conclusion, the inaccuracy of even entirely new anaesthetic gas flowmeters is considerable. For research purposes where flowmeter accuracy is crucial they are inapplicable. For clinical anaesthesia in general the accuracy is not quite satisfactory, and for closed circuit anaesthesia with low fresh gas flows it is insufficient. Exact fractions of oxygen in anaesthetic gas mixtures can only be ensured by continuous monitoring with high accuracy oxygen analysers.

REFERENCES

Levy, A. (1964). The accuracy of the bubble meter method for gas flow measurements. *J. Sci. Instrum.*, **41**, 449.

Macintosh, R. R., Mushin, W. W., and Epstein, H. G. (1958). *Physics for the Anaesthetist*, 2nd edn, p. 202. Oxford: Blackwell.

Purnell, H. (1963). *Gas Chromatography*, 2nd edn, p. 253. New York: J. Wiley & Sons.

Sadove, M. S., Thomason, R. D., Thomason, C. L., and Ries, M. (1976). Evaluation of gas flowmeters. *J. Am. Assoc. Nurse Anesthetists*, **44**, 162.

Waaben, J., Stokke, D. B., and Brinkløv, M. M. (1978). Accuracy of gas flowmeters determined by the bubble meter method. *Br. J. Anaesth.*, **50**, 1251.

PRECISION DES NOUVEAUX DEBITMETRES A GAZ

RESUME

On a fait des recherches sur la précision de cinq nouveaux débitmètres à oxygène et à protoxyde d'azote en se basant sur la méthode du compteur à bulles. Les résultats ont été comparés à ceux que l'on avait précédemment obtenus avec les débitmètres retirés de l'usage clinique. Les nouveaux débitmètres à oxygène ont accusé moins d'erreurs que les anciens. On n'a trouvé aucune différence entre les divers débitmètres à protoxyde d'azote. On a prouvé qu'il y avait des erreurs inacceptables lors des préréglages d'oxygène inférieurs à 1 litre mn^{-1}, ce qui laisse penser que le dosage dans les limites de cette plage n'est d'aucune valeur. Des déviations marquées supérieures aux limites déclarées par les fabricants sont encore constatées à des préréglages supérieurs à 1 litre mn^{-1}. Si l'on veut obtenir un $F\text{I}_{\text{O}_2}$ exact, il y a lieu d'exercer une surveillance continue à l'aide d'un analyseur d'oxygène de très haute précision, même lorsqu'on utilise des débitmètres du nouveau type.

GENAUIGKEIT NEUER GASDURCHFLUSSMESSER

ZUSAMMENFASSUNG

Die Genauigkeit von fünf neuen Sauerstoff- und Stickoxyd-Durchflussmetern wurde mit der Bläschenmeter-Methode untersucht. Resultate wurden mit denen verglichen, die vorher in aus dem klinischen Gebrauch zurückgezogenen Durchflussmessern gefunden wurden. Die neuen Sauerstoffmesser zeigten weniger Ungenauigkeiten als die alten, wahrend es bei Stickoxydmessern keine Unterschiede gab. Unakzeptable Irrtümer zeigten sich bei Sauerstoff-Voreinstellungen unter 1 Liter min^{-1}, so dass sich also erweist, dass Einstellungen in diesem Bereich wertlos sind. Deutliche Abweichungen uber die von den Herstellern angebenen hinaus konnten auch bei Voreinstellungen uber 1 Liter min^{-1} nachgewiesen werden. Ist ein exaktes $F\text{I}_{\text{O}_2}$ erforderlich, dann ist ständige Überwachung mit Präzisions-Sauerstoffanalysatoren unbedingt erforderlich—auch bei neuen Durchflussmessern.

EXACTITUD DE LOS NUEVOS FLUJOMETROS DE GAS

SUMARIO

Se averiguó la exactitud de cinco nuevos flujómetros de oxígeno y óxido nitroso, al usar el método de medición de burbujas. Se hizo una comparación de los resultados con los logrados en flujómetros en desuso clínico. Los nuevos flujómetros de oxígeno registraron menos inexactitudes que los antiguos. No se registró ninguna diferencia en los flujómetros de óxido nitroso. Se demostraron errores inaceptables en níveles prefijados de oxígeno de menos de 1 litro min^{-1}, lo que hace pensar que la graduación dentro de esta margen no tiene valor. Se pudo ver desviaciones marcadas que excedían de los límites declarados del fabricante todavía en níveles prefijados mayores de 1 litre min^{-1}. Si se necesita un $F\text{I}_{\text{O}_2}$ exacto, será esencial una vigilancia continua con un analizador de oxígeno de alta precisión, aún cuando se usan los nuevos flujómetros.

Br. J. Anaesth. (1980), **52**, 101P

EUROPEAN ACADEMY OF ANAESTHESIOLOGY

SCIENTIFIC MEETING

ROYAL POSTGRADUATE MEDICAL SCHOOL, LONDON

OCTOBER 11-13, 1979

PLASMA CONCENTRATIONS OF FENTANYL IN NORMAL SURGICAL PATIENTS AND THOSE WITH SEVERE RENAL AND HEPATIC DISEASE

I. M. CORALL, A. R. MOORE* AND **L. STRUNIN**
*Anaesthetic Department, King's College Hospital and Medical School, London and * Department of Chemical Pathology, The Radcliffe Infirmary, Oxford*

In order to assess the duration of action of fentanyl, plasma concentrations were studied in three groups of patients: 10 normal patients (group I) acting as a control group, group II consisting of five patients with chronic liver disease, and group III 10 patients with end stage renal disease undergoing haemodialysis.

Patients in all three groups were premedicated with oral diazepam 0.3 mg kg^{-1}. Anaesthesia was induced with thiopentone 5.0 mg kg^{-1} and pancuronium 0.1 mg kg^{-1}; the trachea was intubated and intermittent positive pressure ventilation of the lungs instituted. Fentanyl was administered i.v. in the following doses: groups I and III—20 μg kg^{-1}, group II—100 μg per 70 kg. Anaesthesia was maintained with 70% nitrous oxide in oxygen.

Central venous blood samples were taken for plasma fentanyl concentrations before administration of fentanyl (control) and at frequent intervals for up to 4 h after the dose of fentanyl had been administered.

In both groups I and III plasma fentanyl concentration decreased rapidly over the first 30 min, thereafter more slowly. However, plasma fentanyl concentration in the renal group (group III) decreased faster than in the control group I and this difference was statistically significant at most points during the 4 h study period ($P < 0.01$). In group II (patients with chronic liver disease) plasma fentanyl concentration decreased rapidly over the first 20–30 min and thereafter decreased more slowly.

NEONATAL PHARMACOKINETICS OF PETHIDINE (MEPERIDINE) ADMINISTERED TO MOTHERS DURING LABOUR

G. BARRIER, M. TALAFRE AND **J. LASSNER**
Paris, France

Pethidine is administered to women during childbirth both for its analgesic and for its oxytocin properties. The sensitivity of gas chromatography allowed us to study the pharmacokinetics of pethidine in the mother and in the newborn during the first 72 h of life.

Results show widely different uptake of pethidine by the fetus and a much slower urinary elimination in the newborn than in the mother.

The following correlations have been studied:

Blood concentrations (umbilical cord) of pethidine and norpethidine and fetal cardiac rhythm and Apgar score at birth.

Decrease in blood concentrations and urinary excretion of pethidine and the clinical condition of the newborn.

Clinical condition of the newborn and total dose of pethidine received by the mother (obstetric history and modality of birth being taken into account).

Recommendations as to the most appropriate way to administer pethidine have been formulated, depending on the condition of the fetus. The possibility of using a narcotic antagonist is considered.

SOME FACTORS INFLUENCING PLASMA THIOPENTONE CONCENTRATIONS AT WAKING

J. W. DUNDEE, W. A. MCGOWAN, W. TONER AND P. J. HOWARD
Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland

There is a wide scatter in plasma thiopentone concentrations at which patients regain consciousness. In 110 subjects it was found to range from 2 to 22 μg ml^{-1}. The use of opiate or sedative premedication and the fitness of the patients may offer a partial explanation of this phenomenon.

In 1950 Brodie demonstrated that the plasma thiopentone concentration at recovery increased with the induction dose. Dundee, Price and Dripps (1956) confirmed this in man in 18 subjects with a correlation coefficient (r) of 0.94, with doses of thiopentone ranging from 2 to 14 mg kg^{-1} and arterial blood concentrations of 2–24 μg ml^{-1}. The thiopentone concentrations were estimated spectrophotometrically.

With the availability of more sophisticated methods of analysis (Toner et al., 1979) this study was repeated on a larger number of patients using venous blood taken from an antecubital fossa vein. Single doses of 2.5–15 mg kg^{-1} were injected rapidly into 82 fit patients and a blood sample withdrawn from the contralateral arm when they opened their eyes on command. The plasma thiopentone concentrations on wakening ranged from 2 to 31 $\mu g\ ml^{-1}$.

There was a positive correlation between the venous plasma thiopentone concentrations at wakening and the induction dose in $mg\ kg^{-1}$ ($r = 0.69$) and in $mg\ m^{-2}$ ($r = 0.65$). There was a less marked correlation between recovery time and the dose of thiopentone ($r = 0.56$). The table shows some results obtained.

There was an exponential relationship between the plasma concentrations at wakening and the duration of sleep with a relatively shorter time with higher doses. A linear relationship existed between the time to wakening and the $\log_{10}$ plasma concentration at recovery ($r = 0.98$). This is in keeping with the concept of increase in cerebral tolerance with large doses of thiopentone.

TABLE. *Average plasma thiopentone concentrations at recovery and average time to recovery after various doses of thiopentone*

Dose ($mg\ kg^{-1}$)	n	Average plasma thiopentone concn at recovery ± SEM ($\mu g\ ml^{-1}$)	Average time to recovery ± SEM (min)
3.5–5.5	15	7.6 ± 0.7	5.2 ± 0.9
7.5–9.5	14	12.5 ± 1.0	8.6 ± 1.0
11.5–15.0	11	19.1 ± 2.0	13.6 ± 3.1

This study confirms that the induction dose of thiopentone plays a major part in the wide scatter of plasma thiopentone concentrations on wakening.

REFERENCES

Brodie, B. B., Mark, L. C., Papper, E. M., Lief, P. A., Bernstein, E., and Rovenstine, E. A. (1950). *J. Pharmacol. Exp. Ther.*, **98**, 85.

Dundee, J. W., Price, H. J., and Dripps, R. D. (1956). *Br. J. Anaesth.*, **28**, 344.

Toner, W., Howard, P. J., Dundee, J. W., and McIlroy, P. D. A. (1979). *Anaesthesia*, **34**, (in press).

CO_2-BUPIVACAINE FOR CONTINUOUS EXTRADURAL ANAESTHESIA IN OBSTETRICS

W. DICK, E. KNOCHE, E. TRAUB AND P. MILEWSKI
Department of Anaesthesiology, University of Ulm, Western Germany

In a total of 700 patients the effects of either bupivacaine hydrochloride or bupivacaine carbonate were studied within two groups of 350 women each.

The initial doses were usually 20–25 mg in a 0.25% solution, the subsequent amounts ranging from 12.5 to 17.5 mg. In a few cases the concentrations had to be increased to 0.375% or could be decreased to 0.125%.

In group I bupivacaine HCl was administered to 350 individuals, i.e. 19.6% of all parturients. Group II consisted of 31.6% of a total of 1109 parturients. The two groups of patients were almost identical in respect of age, body-weight, risk of birth, number of previous births, gestational age and the indications for extradural anaesthesia.

The mean required total dose of bupivacaine HCl was 63.0 mg per patient, which was followed by adequate pain relief for about 80 min. The mean required dose of bupivacaine-CO_2 was 64 mg. This was almost identical to the HCl group, and was followed by a period of adequate pain relief of 74 min.

Thus we could not find a reduction of the total dose when carbon dioxide was used.

The 1 min Apgar values were slightly better in the CO_2 group than in the HCl group. Newborns, who were severely asphyxiated, were not observed in the CO_2 group compared with those in the HCl group.

An advantage of CO_2-bupivacaine seems to be its greater analgesic effect and the better extension of regional anaesthesia, compared with HCl.

The second main advantage of carbon dioxide solutions, particularly in an emergency in obstetrics, is the interval between the administration of bupivacaine and complete analgesia—3–5 min for carbon dioxide compared with 15–30 min in the HCl group.

We recommend bupivacaine-CO_2 as the local anaesthetic solution of choice for extradural analgesia in obstetrics.

BEHAVIOUR OF THE NEUROMUSCULAR BLOCKADE PRODUCED BY SUXAMETHONIUM OR DIOXONIUM

T. TAMMISTO AND M. SALMENPERÄ
Department of Anaesthetics, University of Helsinki, Finland

The nature of suxamethonium (Sx)-induced "dual block" is disputed. On the other hand, it has been claimed that the dioxonium (Dx)-induced depolarization block soon becomes a stable non-depolarization block (Kimenis, Klusha and Ginters, 1972). It was thought that comparison of blockade by these drugs might yield information on the nature of "dual block". Tubocurarine (dtc) was used for comparison; the series comprised 39 patients. Simultaneous thumb tension and adductor pollicis e.m.g. evoked by indirect stimulation through the ulnar nerve were studied after single (0.1 Hz), train of four (2 Hz) and tetanic (50 Hz) stimulation. With both agents a 90% block in twitch tension was associated with a comparable reduction in e.m.g. with 20% fade in train of four and 60% fade in tetanic stimulation. Maintenance of the block caused an increase in the 2 Hz fade, a reduction in e.m.g. and tachyphylaxis. The 2 Hz fade exceeded 90% in 90 min (10 $mg\ kg^{-1}$) with Sx, and in 60 min (70 $\mu g\ kg^{-1}$) with Dx. With Sx e.m.g. had again recovered to at least 10%, and the need for Sx was reduced by one-third at this stage. With Dx these changes occurred later (Dx 100 $\mu g\ kg^{-1}$) and the decrease in the need for Dx was greater. Thereafter no change in the relationship between these indices was noted and their behaviour resembled blockade caused by dtc. It seems that in the neuromuscular blockade by Sx or Dx three phases can be demonstrated. I: Similar reduction in twitch tension and e.m.g. with distinct 50 Hz but negligible 2 Hz fade. II: More profound reduction in e.m.g. than in twitch tension, tachyphylaxis and gradually increasing 2 Hz fade. III: Fully developed 2 Hz fade, reduction in e.m.g. similar to that in twitch tension and disappearance of tachyphylaxis.

REFERENCE

Kimenis, A. A., Klusha, V. E., and Ginters, Y. A. (1972). *Farmakol. Toxikol.*, **35**, 172.

NO EFFECT OF HALOTHANE ON VARIOUS PARAMETERS OF HUMAN NEUTROPHIL FUNCTION *IN VITRO*

J. F. NUNN, J. E. STURROCK, A. J. JONES, C. O. MORAIN, A. W. SEGAL, S. B. COADE, J. DORLING and D. WALKER
Division of Anaesthesia, Clinical Research Centre, Harrow

It is an unresolved problem whether anaesthetics interfere with body defence mechanisms to infection (see review by Moudgil and Wade, 1976). A logical starting point is the question of whether there is an effect of anaesthetics on neutrophil function *in vitro*. Here, too, there are conflicting reports. The present paper describes a multidisciplinary study of the effect of halothane (mainly at 2% concentration in air) on various aspects of neutrophil function *in vitro*, the cells having been extracted from venous blood samples from normal subjects.

Random movement on glass slides was studied by time-lapse phase-contrast cinemicrography. Halothane 2% produced no significant changes, and this was in contrast to the inhibition of the motility of lymphocytes in a similar preparation (Nunn, Sharp and Kimball, 1970). Random migration through a millipore membrane of 3 μm pore size was significantly increased in the presence of 2% halothane. Migration in response to casein chemotaxis was slightly increased by 2% halothane although the difference did not reach statistical significance.

Electronmicrographs were made of neutrophils fixed 30 s after admixture with latex particles coated with IgG. Phagocytosis was apparently normal in all respects and granules had fused with and discharged their contents into the phagocytic vesicles. The enhanced oxygen consumption associated with this degranulation was measured by polarography and concentrations of halothane up to 3% did not result in any significant difference from control values.

These studies indicate that all the more important aspects of neutrophil function are apparently unaffected by halothane *in vitro* at concentrations equivalent to about 3× minimal alveolar concentration required for anaesthesia. It does not follow that neutrophils from anaesthetized patients do not show impaired function and there are reports of reduced phagocytosis (Cullen, Hume and Chretien, 1975). It seems likely that this is a result of factors other than the effect of the anaesthetic *per se*.

REFERENCES

Cullen, B. F., Hume, R. B., and Chretien, P. B. (1975). *Anesth. Analg.* (*Cleve.*), **54**, 501.

Moudgil, G. C., and Wade, A. G. (1976). *Br. J. Anaesth.*, **48**, 31.

Nunn, J. F., Sharp, J. A., and Kimball, K. L. (1970). *Nature* (*Lond.*), **226**, 85.

COMPARATIVE EFFECTS OF INDUCED HYPOTENSION AND NORMOVOLAEMIC HAEMODILUTION ON BLOOD LOSS IN HIP SURGERY

G. BARBIER-BÖHM, **J. M. DESMONTS**, E. COUDERC, D. MOULIN AND P. PROKOCIMER
Département d'Anesthésiologie, Hôpital Bichat, Paris

Techniques to recover or reduce blood loss during surgical procedures include deliberate hypotension, haemodilution and various methods of autologous blood transfusion. This present study was designed to evaluate blood loss in sodium nitroprusside-induced hypotension and in acute normovolaemic haemodilution associated with autotransfusion. Thirty patients without heart or lung disease were anaesthetized with halothane in nitrous oxide and narcotics for the same surgical procedure (hip arthroplasty). They were divided into three groups: in group I ($n=11$) mean arterial pressure was decreased to 7.05 kPa (55 mm Hg) by sodium nitroprusside infusion. In group II ($n=9$) a volume of 23 ml kg^{-1} of blood was withdrawn just before the surgical procedure under anaesthesia; simultaneously, a volume of 4% albumin solution equal to that of the shed blood and an equal volume of lactated Ringer solution were infused. The shed blood was reinfused after the end of the surgical procedure. Group III ($n=10$) was a control group. Intraoperative blood losses were 1050 ± 185 ml and 900 ± 130 ml in the autotransfused and control groups respectively and 320 ± 35 ml in the hypotensive group. Postoperative blood loss was similar in the three groups. However, the red cell loss was significantly reduced in the hypotensive and autotransfused groups (fig. 1).

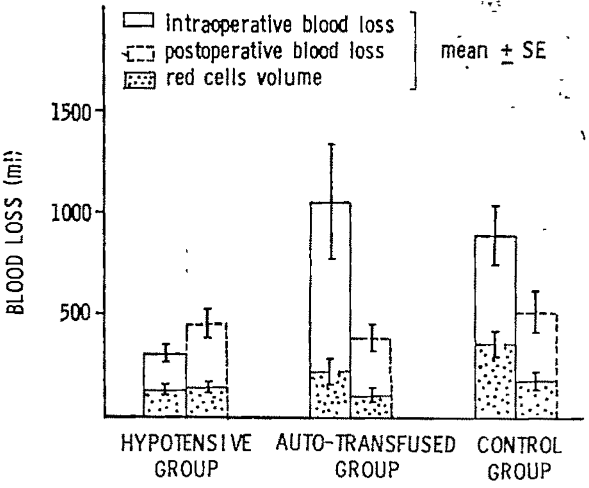


FIG. 1.

Only two patients of the autotransfused group needed an homologous blood transfusion. All patients in the two other groups, except three in the hypotensive group, needed transfusion. The amount of blood transfused was significantly reduced in the hypotensive group: 500 ± 100 *v.* 1485 ± 135 ml in control group.

After the 4th day after operation, there was no significant difference in haemoglobin concentration between the three groups.

The effects of controlled hypotension and acute normovolaemic haemodilution on haemodynamics and oxygen transport were compared. The procedure was well tolerated by both groups. However, the controlled hypotension appeared, in our hands, to be more efficient in reducing the operative blood loss, and the management of this procedure was easier than the normovolaemic haemodilution associated with autotransfusion.

COMBINED THERAPY OF LOW-OUTPUT SYNDROME WITH VASODILATATION AND POSITIVE INOTROPIC STIMULATION IN PATIENTS AFTER OPEN-HEART SURGERY

K. van Ackern, **K. PETER**, and N. Franke,
Institut fur Anaesthesiologie, Klinkum Grosshadern, Munich, West Germany

Postoperative left ventricular failure with a low-output syndrome is a serious complication following cardiac surgery. In this critical situation the stroke volume can be increased by positive inotropic substances but this treatment usually results in an increase in myocardial oxygen consumption. Another therapeutic approach is to improve cardiac function by the use of vasodilators which do not produce a disproportionate increase in myocardial oxygen consumption.

TABLE.

	Control	Dopamine	DOP + SNP + volume
Group I ($n=10$)			
HR	108	112	110
(beat min^{-1})	±14	±8	±10
MAP	62	98*	80
(mm Hg)	±10	±10	±6
CI	1.0	2.4*	3.2*
(litre min^{-1} m^{-2})	±0.3	±0.4	±0.3
PCWP	23	20	19*
(mm Hg)	±2	±3	±3
HR × SAP	9200	13 800*	10 900*
	±1700	±2500	±2000

	Control	SNP + Vol	SNP + DOP
Group II ($n=12$)			
HR	101	98	106
(beat min^{-1})	±12	±8	±17
MAP	105	89*	92
(mm Hg)	±9	±5	±6
CI	2.0	2.8*	3.3*
(litre min^{-1} m^{-2})	±0.3	±0.2	±0.3
PCWP	20	17*	17
(mm Hg)	±3	±2	±1.5
HR × SAP	14 200	11 500	12 900
	±1090	±870	±820

*$P < 0.05$

In the present study the effects on the systemic and pulmonary circulations and myocardial oxygen consumption resulting from combined treatment with vasodilatation and positive inotropic stimulation were investigated in patients with impaired ventricular function after cardiac surgery. Sodium nitroprusside (SNP) was used for vasodilatation, and dopamine as the positive inotropic drug.

Twenty-two patients with a reduced cardiac output were divided into two groups. In group I six patients with aortic valve replacement and four patients with aorto-coronary grafting had a mean arterial pressure (MAP) less than 70 mm Hg whilst in group II, 12 patients with aorto-coronary grafting, the MAP was greater than 70 mm Hg. In all patients the lungs were ventilated with 100% oxygen. The results are summarized in the table.

The first step in treatment is governed by the MAP required to ensure a sufficient degree of myocardial perfusion. In group I MAP was first increased using dopamine. After establishing a sufficient perfusion pressure the dose of dopamine was reduced and the pre- and after-load were decreased by infusion of SNP in increasing doses.

In group II the reduction of pre- and afterload by SNP and the adequate volume supply resulted in an increase of cardiac index (CI) of about 30% without positive inotropic stimulation. An additional small dose of dopamine (5 $\mu g\ kg^{-1}\ min^{-1}$) increased CI finally by 50%.

This combined therapy of postoperative low-output syndrome produced mechanical unloading of the heart by vasodilatation and an increase in cardiac output by positive inotropic stimulation. The heart work was reduced and the myocardial oxygen consumption did not increase disproportionately.

THE EFFECT OF METABOLIC ACIDOSIS AND ALKALOSIS ON LIVER BLOOD FLOW AND OXYGEN CONSUMPTION IN THE GREYHOUND

R. L. Hughes, R. T. Mathie, **D. CAMPBELL** and W. Fitch
University Department of Anaesthesia and Surgery, Glasgow Royal Infirmary, Glasgow

Despite the many advances in the surgery of hepatobiliary disease in recent years, the effect of changes in blood-gas tension and acid–base balance upon liver blood flow and oxygen consumption has been little studied (Greenway and Stark, 1971). In an attempt to remedy this relative deficiency in our knowledge and utilizing recent advances in design of electromagnetic flowmeters, the authors have devised a suitable model in the greyhound (Hughes et al., 1979a, b).

In the present series of experiments hepatic arterial and portal venous blood flow were continuously recorded using Statham SP 2202 electromagnetic flowmeters, mean arterial pressure was recorded via a cannula in the femoral artery and cardiac output was measured by the thermodilution technique, employing a triple-lumen thermistor-tipped catheter placed in the pulmonary artery. Blood samples were taken from the portal vein, the femoral artery and from a hepatic vein. The oxygen content of these samples was analysed using a Lex-O_2-Con Meter allowing hepatic oxygen consumption to be calculated. The effect of metabolic alkalosis, produced by an infusion of sodium bicarbonate, was studied in seven greyhounds and metabolic acidosis, produced by an infusion of lactic acid, was studied in a further series of eight greyhounds.

In the alkalotic group portal venous blood flow and total liver blood flow were significantly increased while hepatic oxygen consumption was unchanged (table). In the acidotic group hepatic arterial blood flow decreased accompanied by an increase in portal venous blood flow resulting in an unchanged liver blood flow. Hepatic oxygen consumption did not change and as an increased proportion of liver blood flow was from the portal vein, hepatic venous oxygen content decreased.

TABLE. *Maximal changes in portal venous flow, hepatic arterial blood flow and total liver blood flow, (ml min^{-1} per 100 g liver) with metabolic acidosis and alkalosis. Values are ± SEM*

	Metabolic acidosis		Metabolic alkalosis	
	Control	Maximum change	Control	Maximum change
Portal venous flow	94.2 ±8.6	126.1** ±9.9	111.7 ±9.3	136.7*** ±10.7
Hepatic arterial flow	35.2 ±14.9	9.6* ±1.1	39.7 ±5.2	48.9 ±7.7
Total liver blood flow	129.4 ±24.4	135.7 ±10.4	151.4 ±12.2	184.5* ±12.5

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

It is concluded that metabolic alkalosis in the greyhound is potentially beneficial to the liver, while metabolic acidosis, by reducing the oxygen available to the liver, appears potentially harmful.

REFERENCES

Greenway, C. V., and Stark, R. D. (1971). *Physiol. Rev.*, **51**, 23.

Hughes, R. L., Mathie, R. T., Campbell, D., and Fitch, W. (1979a). *Br. J. Anaesth.*, **51**, 289.

—— —— —— —— (1979b). *J. Appl. Physiol.*, **47**, 290.

THE INCREASED VASCULAR RESISTANCE IN ATELECTATIC LUNGS: RELATIVE CONTRIBUTION OF ACTIVE VASOCONSTRICTION AND MECHANICAL OBSTRUCTION

L. J. BJERTNAES, R. MUNDAL, A. MAUGE AND A. NICOLAYSEN
Institute of Physiology, Oslo, Norway

It is not known whether the increased pulmonary vascular resistance (PVR) during atelectasis is mainly caused by active vasoconstriction (presumptively induced by hypoxia) or by mechanical obstruction. To study this problem, we have utilized the previous observation that most of the commonly used inhalation anaesthetics inhibit the vasoconstrictor response to hypoxia in ventilated lungs. The effects of halothane, enflurane, and diethyl ether on PVR in atelectatic lungs have been investigated. Two pairs of isolated rat lungs were perfused in series ("cross perfusion") at constant flow. The baseline PVR was determined whilst both pairs of lungs were ventilated with 95% oxygen. One pair of lungs was then made atelectatic by airway occlusion whilst the other pair was ventilated with 2% oxygen. This caused PVR to increase gradually in both preparations. When the maximum PVR was reached in the atelectatic lung pair, one of the above inhalation anaesthetics was administered to the ventilated lungs. The anaesthetic thus reached the atelectatic lung pair via the blood stream. This resulted in a dose-dependent reversible reduction of PVR in the atelectatic lungs. The same effect was obtained by increasing the Po_2 of the blood supplying the atelectatic lungs to more than 66 kPa. Histological examination after perfusion fixation revealed that two of four preparations were completely atelectatic 1 h after airway occlusion, whereas nearly complete atelectasis was obtained in the other two.

In two other groups of experiments, baseline PVR was determined as described above. In the first group the airways were then kept occluded for 1 h. During this period PVR increased by 163% (median). When subsequently the perfusate Po_2 was increased from the previously low value, PVR decreased to 50% (median) above baseline. In the second group, papaverine was added to the perfusate before starting the 1-h period of airway occlusion. During this period PVR increased by 10% (median). When the perfusate Po_2 was increased in this group, no reduction of PVR occurred. Comparison of the two groups suggests that, in this experimental model, mechanical obstruction accounts for about 6% (10/163) of the overall increase in PVR during atelectasis.

ANAESTHETIC MANAGEMENT OF TRACHEAL SURGERY USING THE NEODYNIUM YTTRIUM ALUMINIUM GARNET LASER

G. VOURC'H, M. L. TANNIÈRES, L. TOTY AND C. PERSONNE
Institut d'Anesthésiologie, Paris

Microlaryngeal surgery using a carbon dioxide (CO_2) laser is now a well established procedure. The advantages of a laser are the absence of bleeding and oedema and early cicatrization. One of the risks is the ignition of unprotected rubber or plastic tubes, and of anaesthetic gases, owing to the intense heat generated by the laser beam. The extension of the CO_2 laser to the trachea and bronchial tree raises new problems, since the beams travel, like light, in a straight line and cannot, therefore, reach lesions situated deep within the air passages. One case only (Laforest, 1976) has been published of tracheal dilation using the CO_2 laser. The neodynium yttrium aluminium garnet laser (NYAG) overcomes this difficulty, since the beam is carried through a flexible fibre, and can be aimed in any direction under bronchoscopic control.

The procedure is painless and may be carried out under topical analgesia and sedation in some cases. In order to provide complete immobility general anaesthesia is usually necessary, using total intravenous anaesthesia and a suxamethonium infusion. Ventilation is achieved by a modification of the Sanders' injector, through a side-tube welded to the bronchoscope and opening within its lumen at the tip. No inflammable gases can be used (O_2 or N_2O), but a mixture of 50% nitrogen and oxygen was found to be safe.

In adults the laser flexible fibre can be introduced in a fibreoptic bronchoscope inserted within a large cuffed tracheal tube through a rubber diaphragm and ventilation achieved with enriched air by manual compression of a breathing bag.

The NYAG laser has been used for the excision of benign or malignant tumours in the trachea or bronchi, and of scar tissue resulting from tracheotomy or prolonged intubation, sometimes as a life-saving procedure.

Our results will be presented and discussed.

ACTION OF NARCOTIC AND ANAESTHETIC DRUGS ON CONTRACTILITY OF HUMAN BRONCHIAL MUSCLES

A. Rothhammer, W. Skrobek, E. Schmidt, P. Bruch and **K. H. WEISS**
Institut für Anaesthesiologie der Universität Wurzburg, West Germany

The ventilation of the lung is influenced by the tension of bronchial muscle. Clinical and experimental investigations have shown that narcotics and anaesthetics have an influence on motor activity of bronchial muscle, but there is no common agreement about the action of different substances.

The present report describes *in vitro* studies on human bronchial muscles performed immediately after the operative resection of a part of the lung.

The bronchial muscles were cut into small strips which were extended in a Tyrode organ bath to isometric contraction. The strength of contraction was controlled by depolarization with a potassium-rich Tyrode solution, the different anaesthetics acting directly via the bath solution. Fentanyl, ketamine, thiopentone and droperidol did not change the basic tension. A histamine-induced contraction of bronchial muscle was relaxed in a dose-dependent manner by ketamine, droperidol and thiopentone. Fentanyl was ineffective. The effect of ketamine was immediately reversible whereas thiopentone acted longer.

Studies with volatile anaesthetics are in progress. Halothane and enthurane depress basic tension. The contractility after depolarization was much more depressed by halothane than enflurane.

THE ASPIRATION SYNDROME PATHOPHYSIOLOGICAL ASPECTS OF THE EARLY STAGE

V. Draxler and **K. STEINBEREITHNER**
Boltzmann Institute and Institute of Experimental Anaesthesia, University of Vienna Medical School, Austria

During an investigation to find a model of lung damage for the evaluation of different ventilatory support techniques 15 mongrel dogs were anaesthetized with pentobarbitone 30 mg kg^{-1} and diallylnortoxiferine 0.2 mg kg^{-1} and the lungs ventilated artificially with IPPV ($F\mathrm{I}_{\mathrm{O}_2} = 0.6$). Heart rate (HR), mean arterial pressure (MAP), pulmonary artery pressure (PAP), right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) and static compliance (C_{stat}) were measured and systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and left and right ventricular stroke work index (LVSWI, RVSWI) were derived using appropriate formulae. All measurements were made before and 5 min after the instillation of 1.5 ml kg^{-1} of 0.1 N HCl with pepsin (400 mg per 10 ml) to each lung. Measurements were repeated 1 and 2 h later.

An immediate decrease in HR (13%, $P < 0.0005$) and CI (40%, $P < 0.00005$) with a simultaneous increase of mean pulmonary artery pressure (73%, $P < 0.001$) and PVR (375%, $P < 0.01$), PCWP remaining unchanged, suggested a neuro-reflex mechanism for these haemodynamic changes. A sudden reduction in C_{stat} (38%, $P < 0.005$) suggested reflex bronchospasm. These findings agree with those of Halmagyi and others (1964) who studied the effects of aspiration of fresh and sea water in sheep. These changes may be reduced by the administration of high doses of atropine, but not by bilateral cervical vagotomy; a local parasympathetic reflex mechanism is assumed (Halmagyi et al., 1964).

REFERENCE

Halmagyi, D. F., Colebatch, H. J. H., Starzecki, B., and Horner, G. J. (1964). *J. Appl. Physiol.*, **19**, 105.

OPTIMUM FRESH GAS AND VENTILATORY REQUIREMENTS DURING CONTROLLED VENTILATION WITH T-PIECE SYSTEMS

C. M. CONWAY
Magill Department of Anaesthetics, Westminster Hospital, London

Examination of gas disposition during controlled ventilation within both conventional and coaxial (Bain type) T-piece systems has shown a marked tendency towards complete mixing of fresh and expired gas within the tubing and reservoir bag of the system. Under such conditions if a steady state is assured and the character of inspiratory flow known, values of fresh gas flow ($\dot{V}\mathrm{F}$) and minute volume ($\dot{V}\mathrm{E}$) necessary to produce any required alveolar CO_2 concentration ($F\mathrm{A}_{\mathrm{CO}_2}$) can be calculated. The curves so produced are hyperbolic in nature, the major determinant of the position of any $F\mathrm{A}_{\mathrm{CO}_2}$ isopleth on a $\dot{V}\mathrm{F}/\dot{V}\mathrm{E}$ plot being the time fraction of the respiratory cycle during which alveolar filling is occurring. The predicted values of $\dot{V}\mathrm{F}$ and $\dot{V}\mathrm{E}$ for a square-wave inspiratory flow correlate closely with reported results of practical evaluations of coaxial T-piece systems during controlled ventilation.

An infinite number of combinations of $\dot{V}\mathrm{F}$ and $\dot{V}\mathrm{E}$ can be chosen to produce the same predicted $F\mathrm{A}_{\mathrm{CO}_2}$. In clinical use there are many sources of error likely to affect the accuracy of such predictions. These errors will concern the prediction and delivery of both $\dot{V}\mathrm{F}$ and $\dot{V}\mathrm{E}$. The total error can be minimized by choosing values of $\dot{V}\mathrm{F}$ and $\dot{V}\mathrm{E}$ derived from the point on a CO_2 isopleth with a slope of -1. For $P\mathrm{CO}_2$ of 5 kPa this is equivalent to $\dot{V}\mathrm{F}$ 1.25 times and $\dot{V}_E$ 1.5 times resting minute volume. In adults such flows will be achieved with $\dot{V}_F$ 100 ml kg^{-1} min^{-1} ATPD and $\dot{V}_E$ 120 ml kg^{-1} min^{-1} BTPS. Much larger flows relative to body weight will be needed in children.

EFFECTS OF EXTRA-CORPOREAL CIRCULATION ON THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

J. L. Arroyo, **M. A. NALDA**, R. Perez, R. Llorens and F. Carrascosa
Universities of Navarra and Barcelona, Spain

Valve replacement under extra-corporeal circulation (CEC) was undertaken in 30 patients with aortic valve disease.

The patients were anaesthetized using a thiopentone-nitrous oxide-pancuronium technique with morphine 1.2–1.5 mg kg^{-1}.

At previously determined intervals we measured plasma concentrations of aldosterone (AP), plasma renin activity (ARP), ACTH, growth hormone (HC), cortisol, Na^+, K^+ creatinine and osmotic pressure. The last four substances were determined in urine samples also along with the excretion of noradrenaline and adrenaline.

The results revealed a significant increase of AP, ARP and ACTH during sternotomy. During the period of CEC, the plasma concentrations of ARP increased greatly while mean values of AP and ACTH changed only slightly.

Following CEC, AP increased significantly, while ARP decreased slightly but remaining greater than the value during sternotomy. ACTH decreased to less than mean basal value. There was no correlation between plasma Na^+, K^+ and AP.

We conclude that the exclusion of the pulmonary circulation during CEC limits the conversion of angiotensin I to angiotensin II, which takes place in the lungs by action of dipeptidildipeptidase.

Following CEC our observations revealed the important action of ARP in increasing the aldosterone secretion during open-heart surgery.

IS DEPRESSION OF INSULIN SECRETION DURING ANAESTHESIA A HYPERSENSITIVITY PHENOMENON?

F. CAMU
Department of Anaesthesia, Academisch Ziekenhuis V.U.B., Brussels

Halothane and enflurane anaesthesia impair glucose-stimulated insulin secretion in man and dog. The role of the adrenergic receptors and the cAMP system, in dogs, will be reported.

Insulin secretory response to several insulinotropic agents (glucose, tolbutamide, glucagon, theophylline, isoproterenol) was examined in 10 trained dogs studied awake, anaesthetized with halothane (1.5 vol%) or enflurane (3.0 vol%) in a randomized manner. Cardiovascular measurements, blood-gas status and temperature were monitored continuously and maintained constant during the procedures.

Anaesthesia impaired not only the basal insulin secretion but also the pancreatic response to a glucose pulse or a tolbutamide injection. A phentolamine infusion (10 μg kg^{-1} min^{-1}) significantly increased basal plasma insulin concentrations in awake and anaesthetized dogs. Also, the insulin response to a glucose challenge, which remained unchanged in the awake animal, was clearly improved to normal during halothane or enflurane anaesthesia.

Since α-adrenergic-mediated inhibition of insulin secretion has been attributed to a decrease in islet cAMP concentration, the insulinotropic effects of various stimulators of the adenylate cyclase–cAMP–phosphodiesterase system were tested. Theophylline, a phosphodiesterase inhibitor, improved the insulin output only slightly during anaesthesia. Following i.v. injection of glucagon 1 mg, an adenylate cyclase stimulant, insulin secretion was more impaired during halothane anaesthesia than with enflurane anaesthesia.

Isoproterenol, an adrenergic β-receptor stimulant inducing cAMP generation in pancreatic islets *in vitro*, produced similar peak insulin secretions in awake and anaesthetized animals. This isoproterenol effect was not enhanced by phentolamine but obliterated by β-adrenergic blockade. Propanolol alone did not influence basal insulin secretion nor the insulin response to glucose.

Since halothane and enflurane anaesthesia do not produce an increased concentration of circulating catecholamines, these data are compatible with a change in pancreatic β-cell adrenergic receptor properties similar to that seen in denervation of endocrine tissues.

GENERAL ANAESTHESIA IN "INDUCIBLE" PORPHYRIAS

P. Mustajoki and **J. HEINONEN**
Helsinki, Finland

Acute intermittent porphyria (AIP) and variegated porphyria (VP) are inherited metabolic diseases which occasionally present with acute abdominal and neuropsychiatric symptoms. It is assumed that these symptoms are often induced by certain drugs. The drugs most commonly associated with acute symptoms are the barbiturates. During a survey of porphyria in Finland we discovered occasional cases in which thiopentone had been administered without adverse effects. This led us to study systematically the risk of our patients developing symptoms after general anaesthesia.

We analysed retrospectively 78 anaesthestics given to 47 patients, 33 with AIP and 14 with VP. Sixty-two anaesthetics, 29 including a barbiturate, were given to 37 patients who had no porphyria symptoms at the time of operation. None developed an acute attack after operation. Sixteen anaesthetics were given during an acute attack to 14 patients; 12 received precipitating drugs other than anaesthetics. Porphyric symptoms worsened in 7 of the 10 patients who received thiopentone and in two of the four patients who did not receive thiopentone.

Induction of porphyric symptoms by thiopentone or other anaesthetics, when given in a latent stage of "inducible" porphyria, must be exceptional. However, in practice, it may be wise, even in latent porphyria, to avoid anaesthetics which are known to induce porphyrin synthesis because alternative agents are available.

PLASMA VISCOSITY AND CREMOPHOR-DISSOLVED ANAESTHETICS

L. Gramstad and **J. STOVNER**
Department of Anaesthetics, University Hospital, Oslo, Norway

During induction of anaesthesia we observed that the flow of blood from a plastic cannula in a cubital vein increased considerably after injection of a certain group of anaesthetics: propanidid (Epontol, Bayer), alphaxalone/alphadolone (Althesin, Glaxo) and diazepam (Stesolid, MR Dumex). These drugs are all dissolved in 20% cremophor EL. When these drugs were added *in vitro* to plasma in concentrations equal to those obtained *in vivo*, a 45% reduction in plasma viscosity at shear rate 11.5 s^{-1} occurred. In patients given cremophor anaesthetics to induce sleep, plasma obtained 5 min after injection showed a mean reduction in viscosity of 42% compared with the pre-induction values. The effect on viscosity after a single dose disappeared in 50 min. Triton X-100 added to plasma *in vitro* caused a similar viscosity reduction as cremophor. Interactions *in vitro* of cremophor and Triton X-100 with concentrated urea were similar. This suggests that cremophor *in vivo* protects the protein molecules and perhaps also the cell membranes with a sheet of structured water.

DEVELOPMENT OF NEW STEROID MUSCLE RELAXANTS

J. F. CRUL and N. Krieg
Nijmegen, Netherlands

With the introduction of pancuronium bromide an almost ideal muscle relaxant seemed to have been found. However, over the 12 years of its clinical application several undesirable features became apparent: slow onset of action, tachycardia by vagolysis, medium duration of action, cumulation in patients with impaired renal function.

In particular, the slow onset, the tachycardia and duration of action warranted further study in the search for better steroid muscle relaxants. During an extensive screening of several series of homologues it was found that vagolysis was caused by the A-ring of the steroid molecule, resembling the acetylcholine molecule, and the D-ring was responsible for its neuromuscular blocking potency. The elongation of the acetyl moieties on C3–17 did not improve potency or duration.

The monoquaternary homologue of pancuronium, NC 45, proved the hypothesis by being devoid of vagolytic action. All three transmitter sites (heart, vagus and sympathetic nerves) at which pancuronium caused an inhibitory effect were unaffected, even by large doses of NC 45.

Its greater lipid solubility is probably the reason for its shorter clinical onset time than that of pancuronium.

Intubating conditions were ideal within 120 s with twice the 95% blocking dose. The greatest advantage was its short duration of action. A 95% blocking dose had a recovery index of only 9.7 min compared with 32 min for pancuronium. Repeated doses caused no cumulative effect. Spontaneous recovery rate remained constant after multiple doses. Antagonism with esterase inhibitors was prompt and total.

Metabolism takes place both by alkaline and enzymatic breakdown; $T_{\frac{1}{2}}\beta$ was 5 min in dogs, compared with 7 minutes for pancuronium. It is expected that substitution of the acetyl group in the C17 position by longer chains may increase breakdown even more and provide steroid relaxants of even shorter duration of action.

POSTER PRESENTATIONS

S. DEA-KAMVYSSI	The effect of progesterone on duration of action of hexobarbitone.
S. GASSNER and M. Manoach	The effect of catecholamines on QRS amplitude.
W. JURCZYK and R. Szulc	Influence of halothane upon the bioelectrical function and ultrastructure of the frog skin epithelium under hypercarbia.
P. K. KANIARIS, M. Batrinos, D. Varonos and A. Fasoulaki	Dissociative anaesthesia and hypothalamo–hypophyseal response.
D. KETTLER and J. Teichman	Intentional isovolaemic haemodilution: haemodynamics, myocardial oxygen demand, tolerance to hypoxaemia and pulmonary gas exchange.
P. LOTZ, H. Oesterle, and F. W. Arnefeld	CPAP versus IPPB. Comparative investigations in healthy adults.
C. MANNI	An outline for general education and training in medical emergency.
M. A. NALDA and M. S. Carrasco	First studies of a new molecule, MA-14012-4.
G. P. NOVELLI, E. Pieraccioli, V. A. Peduto, and F. Festimanni	Antalgic effect of aprotinin in the rat and its prevention by naloxone.
C. PRYS-ROBERTS, J. W. Sear and J. M. Chapman	Cardiorespiratory responses to induction and maintenance of anaesthesia with minaxolone, a new steroid anaesthetic.
M. ROSEN and M. D. Vickers	Self-administration of an analgesic drug.
J. SAINT-MAURICE, J. P. Loose and P. Plouin	The e.e.g. during Ethrane anaesthesia in children.

LABORATORY DEMONSTRATIONS

M. K. Chakrabarti	Ventilator testing.
J. G. Whitwam and W. A. C. Scott	Fentanyl and vagal baroreceptor interaction during nerve stimulation.
M. K. Sykes and C. Orchard	The effect of anaesthetic and inotropic drugs on the response of the pulmonary circulation to hypoxia.
R. Sanchez de Leon	The measurement of oncotic pressure.
G. M. Hall	Porcine malignant hyperthermia.
J. Patterson	Progressive depletion of plasma cholinesterase during daily plasma exchange.

Printed in Great Britain by John Wright and Sons Ltd at The Stonebridge Press, Bristol BS4 5NU

© Macmillan Journals Ltd 1980

THE HOWORTH ACTIVE SCAVENGING SYSTEM FOR ANAESTHETIC GAS POLLUTION

The Howorth anaesthetic gas scavenging system is an active system designed specifically to reduce air pollution by anaesthetic gases to well below the maximum levels recommended by N.I.O.S.H. in the U.S.A. and by the British Association of Anaesthetists in the U.K. The system complies with the principles of D.H.H.S. Circular HC(76)38.

SYSTEM CHARACTERISTICS

High Volume, Low Pressure

The high volume ensures high dilution of gases and all moisture, thus avoiding explosion risk and any condensation within the ducts.

No excessive or dangerous suction pressure can be exerted on the anaesthetic machine circuits.

There is no imbalance of pressure if only one extract point is being used on a multi-point system.

Versatility of Function

This system is applicable to any anaesthetic circuit and any type of ventilator also, with an adaptor, for dentistry and pediatrics.

Break Point Connections

These are designed to limit the suction pressure on the machine circuits to the required and recommended limit of 0.5 cm/H_2O.

They cannot be occluded accidentally.

They are compatible with 18 mm, 22 mm or 30 mm extract hose and they are capable of exhausting peak flows of up to 300 litres per minute.

Multi-Purposes Application

The system is designed to cope with extracts from anaesthetic rooms and also to exhaust the patient's breath in recovery rooms.

Versatility of Layout Design

The system can be adapted to scavenge simultaneously, for example, four anaesthetic machine points, or three or four recovery room points, or combinations of machine and recovery room points.

Each extract point is fitted with a self-closing valve which enables alternative extract points to be installed on the same fan system.

Inbuilt Safety Factors

A failure light on the control and indicating panels is activated by an air flow sensor fitted to the fan.

The fan motor is outside the air stream, and the fan blades are of non-ferrous material.

Should the fan motor fail, the system can still operate, as a temporary measure, as a passive system without adversely affecting the anaesthetic circuits.

Typical Test Results

Hospital 'A'
Operating Theatre—no scavenging: 600–1000 ppm N_2O
passive system: 230–300 ppm N_2O
Howorth system: 0–3 ppm N_2O
Comment: The 3 ppm were traced to leaks in the anaesthetic circuitry.

Hospital 'B'
Operating Theatre—no scavenging: 800–1000 ppm N_2O
Howorth system: 0–6 ppm N_2O
Comment: The 6 ppm were traced to a leaking cuff on the endotracheal tube.

We should be pleased to offer any further information on request.

HOWORTH SURGICAIR

Lorne Street, Farnworth, Bolton. Tel: 0204-71131 Telex: 635242

Design Council Award 1977

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 1 *Published monthly* JANUARY 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120;
Rest of World £27.50, Airmail £50 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

CONTENTS

PAGE

EDITORIAL: Maternal mortality and anaesthesia .. 1
D. D. Moir

EXPERIMENTAL

Dynamic behaviour of the chest and of the abdomen in anaesthetized piglets during rapid insufflation .. 5
M. Arborelius jr and S. Lindahl

Procine malignant hyperthermia. VII: Hepatic metabolism .. 11
G. M. Hall, J. N. Lucke, R. Lovell and D. Lister

24-Hour Althesin–fentanyl anaesthesia in dogs. Time course of haemodynamic changes .. 19
G. Michalot, P. Girardet, F. Grimbert, D. Piasentin and B. Stieglitz

Effect of biliary excretion on ketamine anaesthesia in the rat .. 23
S. J. Ireland and A. Livingston

CLINICAL INVESTIGATION

Mass spectrometer measurement of oxygen uptake and carbon dioxide exchange during cardiopulmonary bypass .. 29
T. R. Abbott, B. Goodwin, G. Clark and G. J. Rees

Radial artery cannulation. *A prospective study in patients undergoing cardiothoracic surgery* .. 41
F. M. Davis and J. M. Stewart

Comparison of the effects of spinal anaesthesia and general anaesthesia on postoperative oxygenation and perioperative mortality .. 49
P. J. McKenzie, H. Y. Wishart, K. M. S. Dewar, I. Gray and G. Smith

Lumbar extradural injection pressures in pregnant women. *An investigation of relationships between rate of injection, injection pressures and extent of analgesia* .. 55
R. P. Husemeyer and D. C. White

PAGE

The anaesthetic machine—a study of function and design .. 61
G. Boquet, J. A. Bushman and H. T. Davenport

Neuromuscular blockade by neostigmine in anaesthetized man .. 69
J. P. Payne, R. Hughes and S. Al Azawi

Complement-mediated reactions to diazepam with Cremophor as solvent (Stesolid MR) .. 77
M. S. Hüttel, A. Schou Olesen and E. Stoffersen

Effects of doxapram on postoperative pulmonary complications following thoracotomy .. 81
P. S. Sebel, E. J. Kershaw and W. S. Rao

Evaluation of glycopyrrolate and atropine as adjuncts to reversal of non-depolarizing neuromuscular blocking agents in a "true-to-life" situation .. 85
D. A. Cozanitis, J. W. Dundee, J. D. Merrett, C. J. Jones and R. K. Mirakhur

I.v. practolol during microlaryngoscopy. Effect on arterial pressure, heart rate, blood glucose and lipolysis .. 91
O. Werner, J. Magnusson, R. Fletcher, P. Nilsson-Ehle and O. Pahlm

APPARATUS

Accuracy of new gas flowmeters .. 97
J. Waaben, M. M. Brinkløv and D. B. Stokke

ABSTRACTS

Proceedings of the European Academy of Anaesthesiologists, London Meeting, October 11–13, 1979 .. 101

EDITORIAL BOARD page ii

MACMILLAN JOURNALS LTD, 4 LITTLE ESSEX STREET, LONDON WC2R 3LF

12.9.80

Volume 52, No. 2 February 1980

Postgraduate Educational Issue
containing a Symposium on Muscle
Edited by F. R. S. Ellis and J. Norman

British Journal of Anaesthesia

Editor of General Issues: A. A. Spence

Fluothane

the original halothane – purely from ICI

'Fluothane' is a trade mark for Halothane BP
Detailed information is available on request

Imperial Chemical Industries Limited
Pharmaceuticals Division
Alderley Park Macclesfield
Cheshire England

Patients are quick to sit up and take notice after

ALTHESIN

(alphaxalone and alphadolone acetate)

the anaesthetic for short procedures

Recovery is outstandingly good, rapid and progressive

"Althesin appears to be an excellent induction agent."[1]

Althesin provides a rapid and pleasant recovery with a low incidence of hangover.[1]

Patient acceptance is high and the incidence of nausea and vomiting is low.[2]

"Patients from morning lists are quite able to have a full lunch, which they could not have done with any barbiturate."[3]

1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

Glaxo

Glaxo Laboratories Limited
Greenford, Middlesex
UB6 0HE

Althesin is a Glaxo trade mark

Induction of anaesthesia
Maintenance of anaesthesia
Experience is insufficient at present to advocate use of Althesin in infants under one year, in patients with hepatic dysfunction, and for maintenance of anaesthesia in obstetrics.

Dosage and administration
As usual, it is recommended that patients should fast before receiving Althesin.
The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e., half to three-quarters of a millilitre per 10kg.
Younger children usually require the higher dose and may need 0·075ml/kg bodyweight. Althesin should be injected slowly, taking no less than 30 seconds, as this promotes smooth induction.
Althesin has negligible analgesic activity.

Contra-indications
Previous adverse reactions to Althesin.
Hepatic failure.

Precautions
Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants of the central nervous system may retard recovery of full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume normal activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects
Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, and of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post-operative nausea and vomiting are infrequent. There have been occasional reports of more severe reactions. Bronchospasm and/or a marked drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids and plasma expanders.

Overdosage
If serious respiratory depression occurs, respiration should be supported mechanically. The margin of safety is wide, and 0·2ml/kg, or four times the minimum sleep dose, has been given as a single dose without serious effects.

Packs
Ceramically-printed 5 or 10ml ampoules in boxes of 10 ampoules.

Product Licence number 4/0189
Price to Hospital (exclusive of VAT)
5ml 80p

EDITORIAL BOARD

Editor of General Issues

A. A. SPENCE, *Reader, University Department of Anaesthesia, Western Infirmary, Glasgow*

Editor of Postgraduate Educational Issues

J. NORMAN, *Professor of Anaesthetics, The General Hospital, Tremona Road, Southampton SO9 4XY*

C. M. CONWAY, *Professor of Anaesthesia, Westminster Hospital, London*
E. A. COOPER, *Professor of Anaesthesia, University of Newcastle upon Tyne; Honorary Consultant Anaesthetist, Newcastle University Hospitals*
J. W. DUNDEE, *Professor of Anaesthesia, Queen's University of Belfast*
F. R. ELLIS, *Reader in Anaesthesia, University of Leeds*
W. FITCH (Assistant Editor), *Senior Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*
G. M. HALL, *Senior Lecturer in Anaesthetics, University of London, Royal Postgraduate Medical School*
C. J. HULL, *Senior Lecturer in Anaesthesia, University of Newcastle*
A. R. HUNTER (Chairman), *Professor of Anaesthesia, University of Manchester*
D. G. MCDOWALL, *Professor of Anaesthesia, University of Leeds*
W. W. MAPLESON, *Professor of the Physics of Anaesthesia, Welsh National School of Medicine, University of Wales*
J. F. NUNN, *Head of Division of Anaesthesia, Clinical Research Centre, Harrow; Honorary Consultant Anaesthetist, Northwick Park Hospital*
J. P. PAYNE, *British Oxygen Research Professor of Anaesthetics, Royal College of Surgeons of England*
C. PRYS-ROBERTS, *Professor of Anaesthetics, University of Bristol*
J. E. RIDING (Hon. Treasurer), *Consultant Anaesthetist, United Liverpool Hospitals; Honorary Lecturer in the Department of Anaesthesia, University of Liverpool*
J. G. ROBSON, C.B.E. *Professor of Anaesthetics, University of London, Royal Postgraduate Medical School*
D. B. SCOTT, *Consultant Anaesthetist, Royal Infirmary Edinburgh*
G. SMITH, *Professor of Anaesthesia, The General Hospital, Leicester*
M. K. SYKES, *Professor of Clinical Anaesthesia, Royal Postgraduate Medical School, London*

Editorial Assistants

KIRSTEEN M. S. DEWAR, *Consultant Anaesthetist, Western Infirmary, Glasgow*
G. N. C. KENNY, *Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*

Papers for publication and all editorial communications should be addressed to the Editor, University of Glasgow, Department of Anaesthesia, Western Infirmary, Glasgow G11 6NT; business communications to the publishers: Macmillan Journals Ltd, 4 Little Essex Street, London WC2R 3LF.
The GUIDE TO CONTRIBUTORS can be found on pages x, xii & xiv of the advertisement section of this issue.
Published monthly. Annual subscriptions: U.K. £22·50, U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27·50, Airmail £50; (or equivalent in any other currency). ISSN 0007-0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.
Overseas subscribers may make payments into U.K. Post Office Giro Account No. 519 2455. Full details must accompany the payment.
Second Class Postage Paid New York, N.Y. U.S. Mailing Agent: Expediters of the Printed Word, Ltd, PO Box 1305, Long Island City, N.Y. 11101.

All enquiries concerning advertising should be addressed to
Advertisement Department, Macmillan Journals Ltd, 3 Dyers Buildings, Holborn, EC1N 2NR (Telephone 01-831 6901). © Copyright: Macmillan Journals Ltd, 1980.

12.9.90

RIPPLE
HEAT
RIPPLE
COOL

It is in the interests of both patient and nursing staff that everything possible is done to avoid pressure sores.

Patients are at their most vulnerable when on the operating table. The Gelman Hawksley Ripple Heat Unit relieves pressure and controls temperature loss, this same unit continues to provide care when the patient returns to the ward.

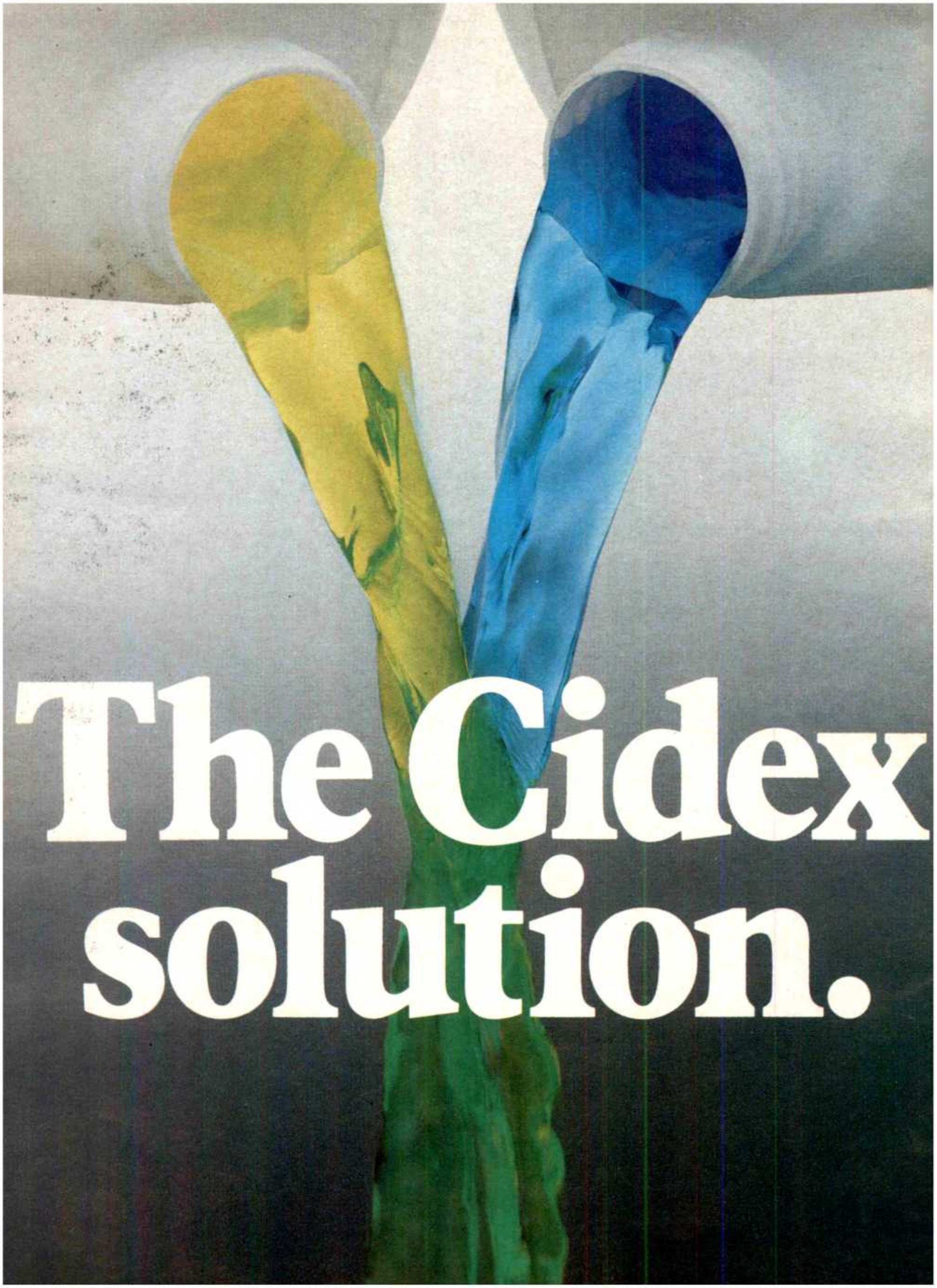
The Gelman Hawksley Ripple Cool is invaluable when cooling techniques are required. This new unit will heat/cool and ripple while controlling temperature within a range of 10°C to 40°C.

Contact us in Northampton, we will be happy to arrange a demonstration.

GELMAN HAWKSLEY LIMITED

UK Sales and Service
10 Harrowden Road. Brackmills
Northampton NN4 0EB
Tel: 0604 65141
Telex: 311871 Gelawk

LIBRARY


The Cidex solution.

It has long been recognised that different hospitals have different disinfection and sterilization requirements.

These differences, of course, arise from the degree of contamination present, the type of equipment and rate of throughput, and the cleaning/drying procedures used.

What hasn't been recognised sufficiently up till now is that these factors combine to have a cumulative effect on the use-life of cold disinfectant solutions–creating a need for solutions with different use-lives.

To meet this need there are now two solutions.
–CIDEX* Activated Glutaraldehyde Solution with a use-life of up to 14 days.
–CIDEX* Long-Life Activated Glutaraldehyde Solution with a use-life of up to 28 days.

New CIDEX* Long-Life Solution has all the trusted and well-proven benefits of 14 day CIDEX* Solution but has an effective life of 28 days where usage factors permit.

A fresh peppermint odour and blue colour differentiate CIDEX* Long-Life from green 14 day CIDEX* Solution.

WHICH CIDEX* SOLUTION TO USE

While the effects of dilution and gross protein contamination are always present, these can be minimal due to low throughput.

Under these circumstances, new CIDEX* Long-Life Solution is much more convenient and can offer substantial cost savings.

In a busy unit, however, where pressures generally do not permit drying, protein contamination and dilution can build up over a period–particularly with bulky items, such as anaesthetic tubing, which have a high carry-over of water.

In situations such as this, 14 day CIDEX* Solution offers complete assurance of its efficacy, assurance which has been confirmed repeatedly all over the world.

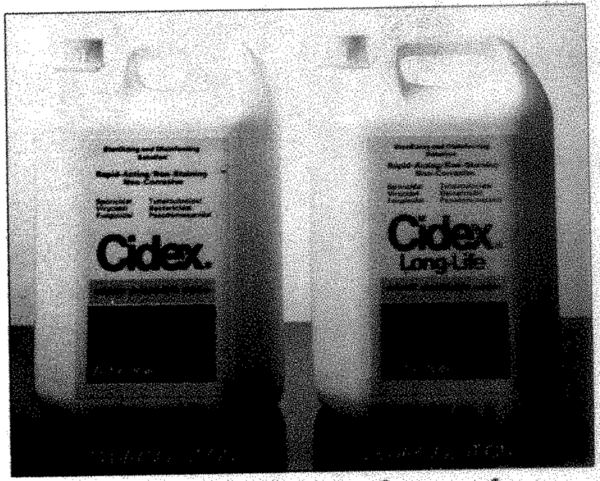
CIDEX* SOLUTIONS. NOT ONLY A CHOICE BUT A BETTER CHOICE

Both solutions have the complete range of cidal activity which has made CIDEX* Solution the prime agent of choice for disinfection and sterilization of heat sensitive and delicate equipment.

Both have the remarkable non-corrosive properties which in laboratory tests have proven them to be less corrosive than deionised water.

14 day CIDEX* Solution in the green container. 28 day CIDEX* Long-Life Solution in the blue container.

Whatever your choice, you can be confident that CIDEX* is the safest, most cost-effective solution to your disinfecting or sterilizing problem.



A choice of CIDEX* solutions from Arbrook – now you can choose wisely.

Arbrook*

Arbrook Products Limited, Livingston, Scotland EH54 7AT *Regd. Trademark © Arbrook Products Limited 1979.

Croydon Postgraduate Medical Centre

DIPLOMA IN ANAESTHETICS COURSE

12th & 13th April 1980

A series of Tutorials will be held in the Postgraduate Medical Centre, Mayday Hospital, Mayday Road, Thornton Heath, Surrey CR4 7YE. Tel: 01-684-6999. Ext: 355.

Details are available from the Medical Centre.

Course is approved for Study Leave for Hospital Doctors.

UNIVERSITY OF OTAGO

The Christchurch Clinical School of Medicine
Christchurch, New Zealand

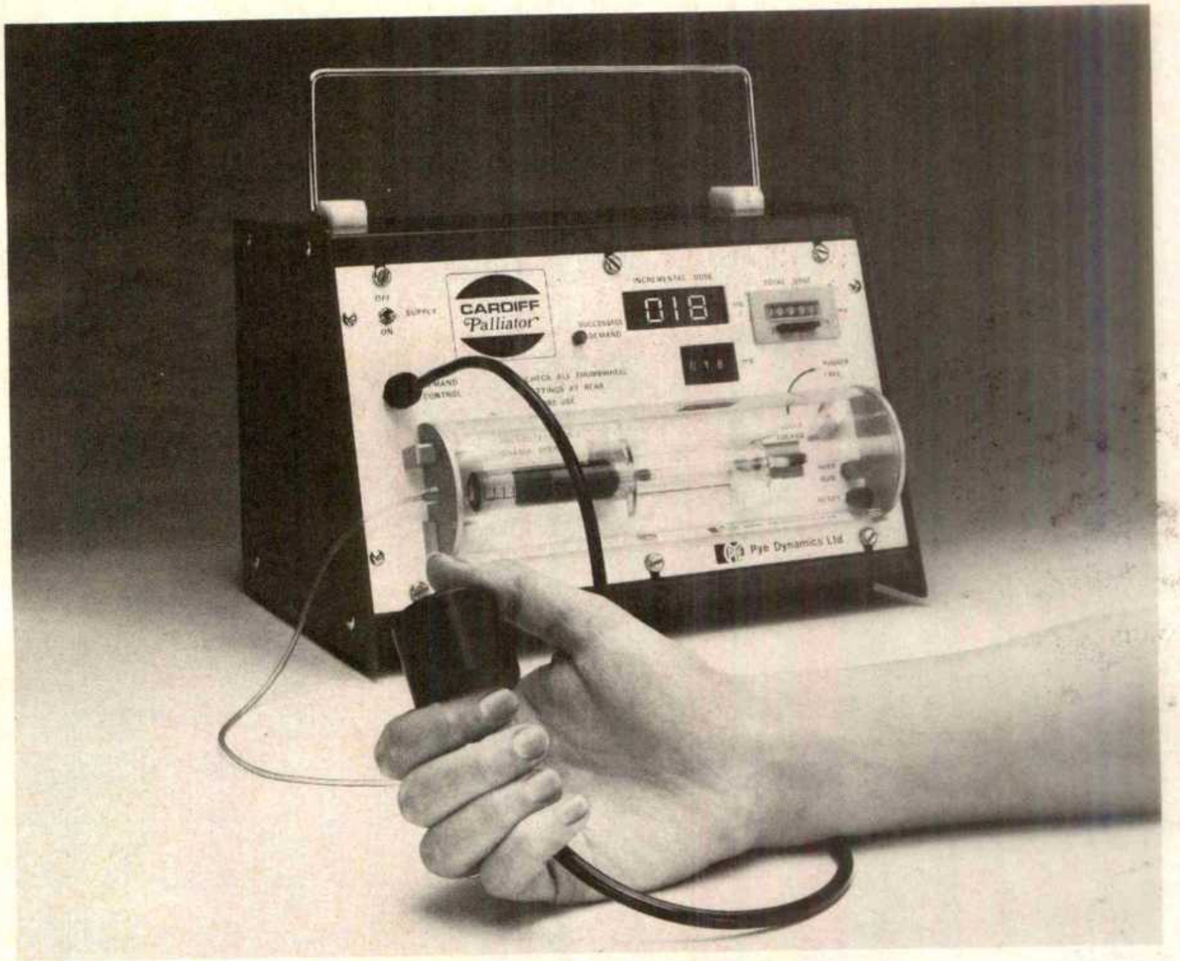
PROFESSOR OF ANAESTHESIA

Applications are invited for the foundation Chair of Anaesthesia in the Christchurch Clinical School of Medicine within the University of Otago.

Salary: Professorial salaries for medically qualified staff are fixed at various points within the present range of NZ$35,032 per annum–$39,069 per annum.

Further particulars may be obtained from the Secretary General, Association of Commonwealth Universities (Appts), 36 Gordon Square, London WC1H 0PF, from the Registrar, University of Otago, P.O. Box 56, Dunedin, New Zealand, or from the Dean, Christchurch Clinical School, Christchurch Hospital, Private Bag, Christchurch, New Zealand.

Application close on 29 February 1980.



The Cardiff palliator.
Safer pain relief when the patient needs it.

The Cardiff Palliator is a patient-controlled syringe driver for the safe administration of intravenous analgesics.

Results show that patients receiving smaller, but more frequent doses of analgesics using the Cardiff Palliator suffer less depression than when it is administered by conventional methods.

Simple and safe
The clinician has total control over presetting the drug concentration, the minimum time interval between doses, actual dose size, and the rate of infusion; thus ensuring that a patient cannot demand more than a safe maximum dose.

To operate, the patient must press the hand-held push button twice within a second, which avoids an accidental dose being delivered. Each dose is indicated audibly and visibly, and a magnetic counter maintains a record of the total dose administered.

For full details on the new Cardiff Palliator for safer, easier pain relief, just contact:

Pye Dynamics Ltd
Pye Dynamics Limited, 459 Park Avenue, Bushey, Herts.,
England WD2 2BW. Telephone: Watford 28566. Telex: 923010.

A member of the Pye of Cambridge Group

SIEMENS

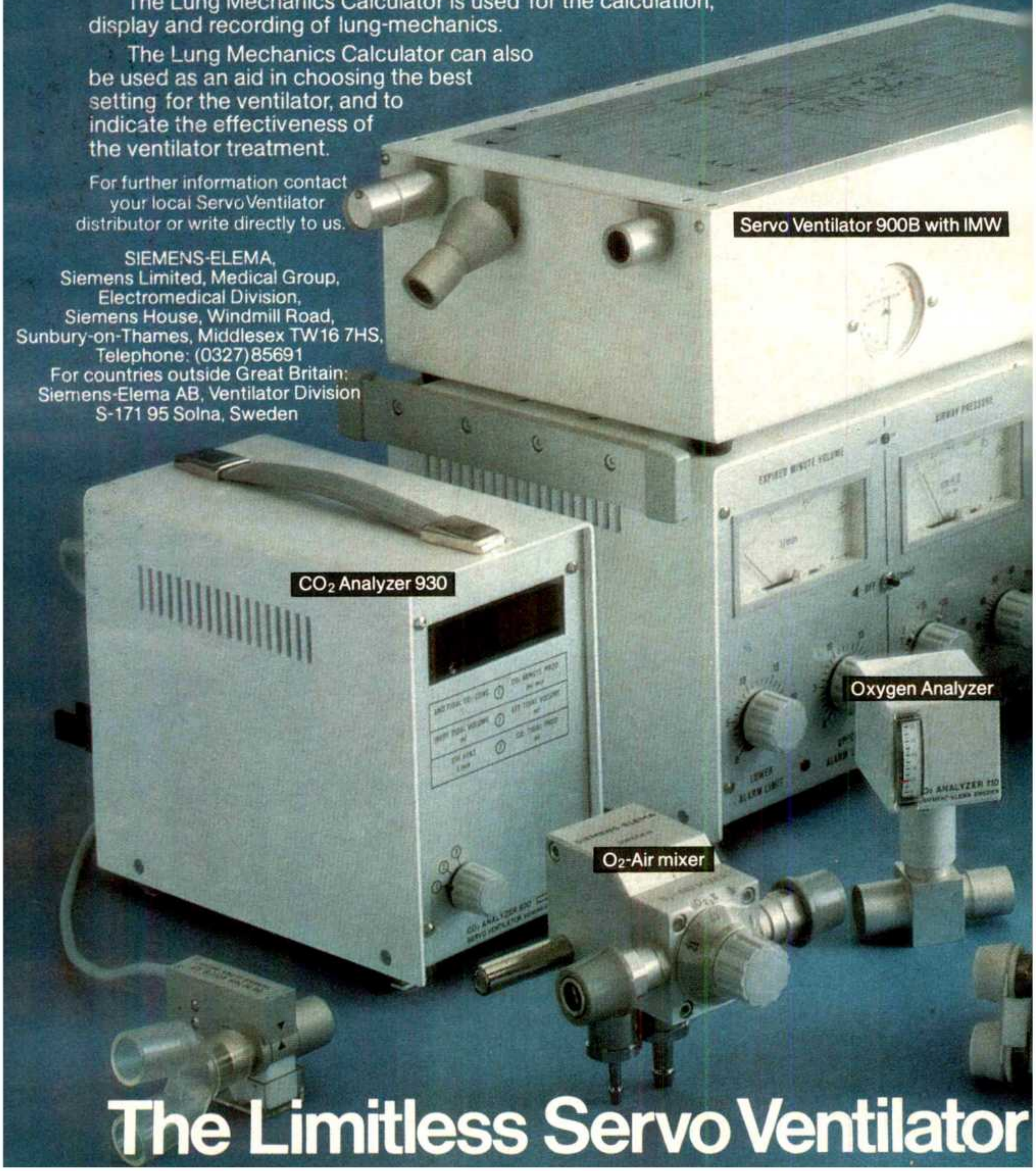
The Lung Mechanics Calcu
Servo Ventilator treatment

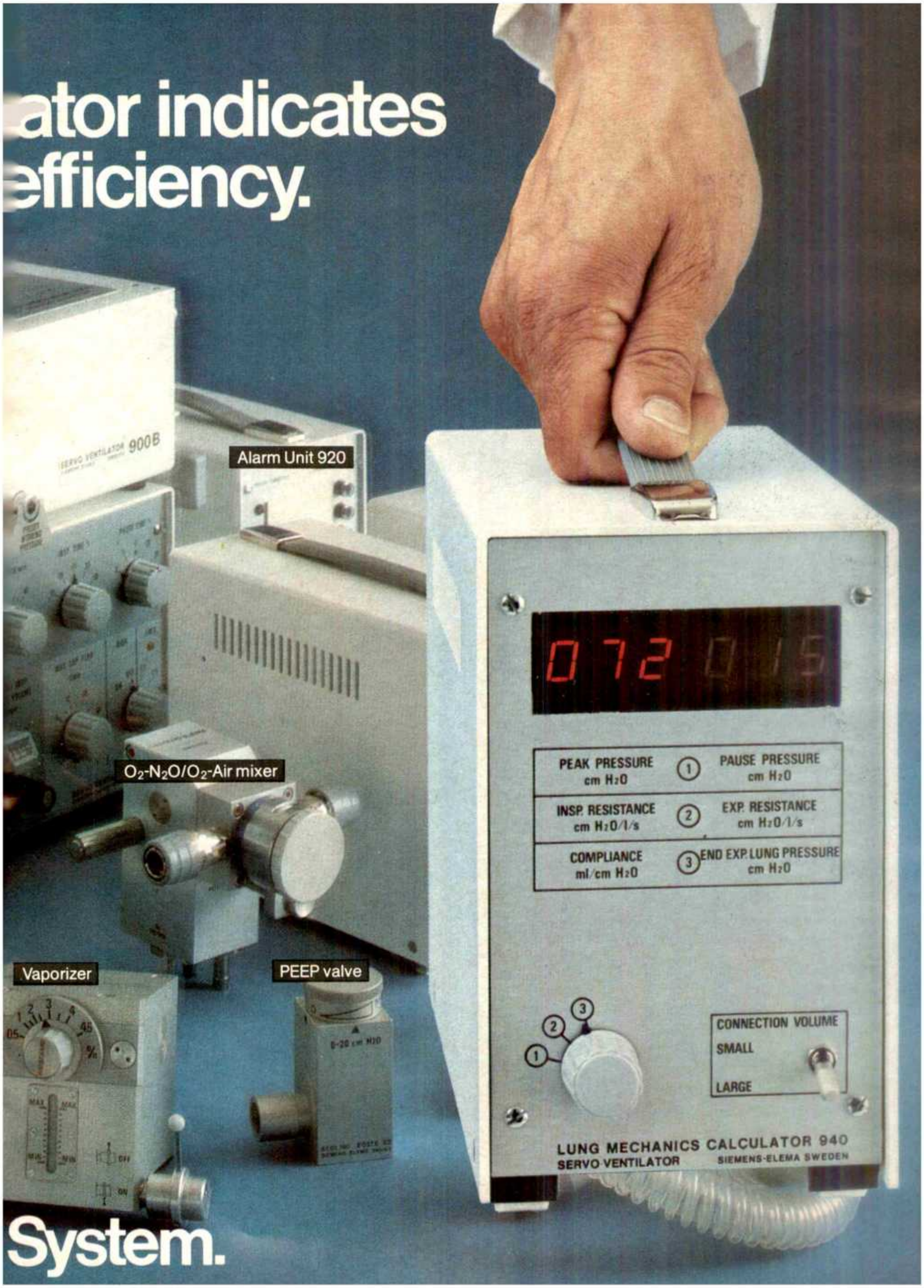
The Lung Mechanics Calculator is used for the calculation, display and recording of lung-mechanics.

The Lung Mechanics Calculator can also be used as an aid in choosing the best setting for the ventilator, and to indicate the effectiveness of the ventilator treatment.

For further information contact your local Servo Ventilator distributor or write directly to us.

SIEMENS-ELEMA,
Siemens Limited, Medical Group,
Electromedical Division,
Siemens House, Windmill Road,
Sunbury-on-Thames, Middlesex TW16 7HS,
Telephone: (0327) 85691
For countries outside Great Britain:
Siemens-Elema AB, Ventilator Division
S-171 95 Solna, Sweden


Servo Ventilator 900B with IMW
CO₂ Analyzer 930
Oxygen Analyzer
O₂-Air mixer
The Limitless Servo Ventilator


ator indicates
efficiency.
SERVO VENTILATOR 900B
Alarm Unit 920
O_2-N_2O/O_2-Air mixer
Vaporizer
PEEP valve
0-20 cm H2O
072 015
PEAK PRESSURE cm H2O
① PAUSE PRESSURE cm H2O
INSP. RESISTANCE cm H2O/l/s
② EXP. RESISTANCE cm H2O/l/s
COMPLIANCE ml/cm H2O
③ END EXP. LUNG PRESSURE cm H2O
CONNECTION VOLUME
SMALL
LARGE
LUNG MECHANICS CALCULATOR 940
SERVO VENTILATOR
SIEMENS-ELEMA SWEDEN
System.

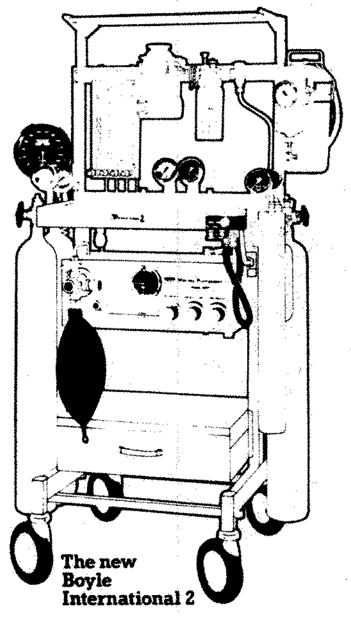
Announcing enormous wait reductions

Boyle anaesthetic machines, suction equipment, oxygen therapy equipment... the products you've been waiting for are now available either ex-stock, or within a steadily reducing delivery period.

Medishield have earned a deserved reputation for quality and dependability; happily we are, once more, able to maintain this reputation, and give you the prompt service which you expect.

For detailed information on delivery of specific products please contact:

BOC (Medishield)
Priestley House, 12 Priestley Way
London NW2 7AG. Telephone: 01-450 8955



The new Boyle International 2

Medishield depend on Medishield

NOW

Medishield reduce the waiting without increasing the price

The benefits of our major factory modernisation programme are not just shorter delivery dates.
As from the 1st January 1980 we are introducing price ruling at the time you place your order. This price will stand regardless of subsequent increases.
We can now offer you a better service than ever before.

Please send me the new
Medishield Product Catalogue

NAME ________________

ADDRESS ________________

____

POSITION ________________

NO JANUARY PRICE INCREASE

Medishield

BOC Medishield, Priestley House
12 Priestley Way, London NW2 7AG Telephone: 01-450 8955

If you haven't much faith in flimsy packs, here's a firm alternative.

The Monoject range of Brunswick syringes and needles are packed in heat/sealed rigid containers to ensure perfect condition. With the heat seal unbroken, only the Brunswick range are guaranteed sterile.

☐ Please send me further details of Spinal needles for routine and specialist procedures.

☐ Please send me samples of Brunswick syringes/needles and blood collection system.

☐ Please send me details of Audio Visual Training and guide to 'The Safe Giving of Injections'.

Name ________________

Position ________________

Organisation ________________

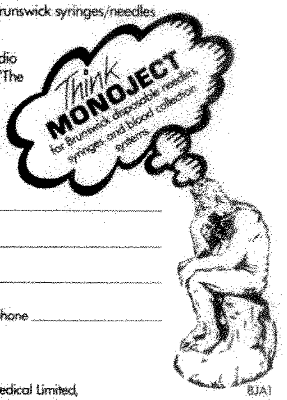
Address ________________

____

MONOJECT
DIVISION OF SHERWOOD MEDICAL

Telephone ________________

The Monoject Division of Sherwood Medical Limited, BJA1
London Road, County Oak, Crawley, West Sussex RH10 2TL Telephone: Crawley 34501


Think
MONOJECT
for Brunswick disposable needles, syringes and blood collection systems.

GUIDE TO CONTRIBUTORS

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. Two issues each year deal mainly with material of postgraduate educational value.

PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publishers.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted.

LEGAL CONSIDERATIONS

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

PREPARATION OF MANUSCRIPT

Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full addresses) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

Title page

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should also be suggested.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the experiments to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of experimental results, while concise, should permit repetition of the experiments by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of

THE ACCUROX**
OXYGEN MASK.
MORE AND MORE
PEOPLE ARE COMING
ROUND TO IT.

"It was found that patients left the ACCUROX** mask in position more frequently than the other…masks, and the Recovery staff did not have to keep replacing it due to the patient having rejected it in their post anaesthetic state."

"…INSPIRON** ACCUROX** masks..(have given).. considerable financial saving, high patient acceptability and reduction in storage space by standardisation on one mask."

Re-cycling oxygen masks in the Recovery Room.
N. Duffin - Nursing Times - 11th May 1978

For further details contact:-

Inspiron**

A Division of C. R. Bard International Limited
Pennywell Industrial Estate, Sunderland SR4 9EW
Tel: 0783 243131

**Trademark

digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

Discussion

The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially.

References

There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

In the case of books, the reference should be as follows: name of author and initials; year of publication in parentheses; title of book, underlined; number of edition; page number; town of origin, publisher; for example: Hill, D. W. (1971). *Physics Applied to Anaesthesia*, 2nd edn, p. 212. London: Butterworths.

The *British Journal of Anaesthesia* should be referred to as *Br. J. Anaesth.*

In the text up to three authors should be named before the use of "... et al.". If reference is made to several publications during a particular year, written by a larger group of authors who have alternated the order of authorship, as many names must be written as are necessary to distinguish between the publications, before use of "... et al." in conjunction with the year suffixes a, b, c.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase "(in press)" replacing volume and page number.

It is essential that authors verify the content and details of references which they list, as this responsibility cannot be accepted by either Editors or Publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ ◐
◑ ◒ ⊙ ⊙ ⦶ ⊕ ⊖ ▩ ■ ▤ × +

The name of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It is emphasized that care taken in the original preparation of figures will obviate the time-consuming and expensive necessity of their revision.

"Minivent" Ventilator

This low cost, easy to handle pocket size, portable ventilator produces completely automatic, reliable and efficient ventilation in anaesthesia. It requires no extraneous power source and fits standard continuous flow anaesthetic machines. Precision manufactured in durable materials . . . . Price £72

MINIVENT KIT consisting of Minivent, non-return valve with catheter mount, reservoir bag, bag mount to fit Boyle's/British Standard machines—all specially designed for use with the Minivent . . . . Price £98

Available on sale or return basis

MINIVENT
(ROOM302
Abbey Life House, 1-3 St. Paul's Churchyard,
London EC4M 8AU (01-248 6724)

GOVERNMENT OF JAMMUAND KASHMIR
INSTITUTE OF MEDICAL SCIENCES
51–52, TULSI BAGH
SRINAGAR

ADVERTISEMENT NOTICE NO: 29 DATED : DEC 4 1979

Institute of Medical Sciences, Srinagar is desirous to fill up senior faculty posts in the following disciplines:-

Cardiac Anaesthesiology, General Anaesthesiology, Resuscitation Anaesthesiology, Neuroanaesthesiology, Blood Transfusion & Immuno-haematology, Clinical Biochemistry, Clinical Pharmacology, Hospital Administration-cum-Medical Superintendent, Bacteriology, Virology, Parasitology, Mycology, Medical Physics, Nuclear Medicine, Radiation Oncology, Cytology, Haematology, Immuno-pathology, Morbid Anatomy, Radio-diagnosis and Community Medicine.

Senior Consultants will be either in the category of professors or associate professors in the scale respectively of 2400–100–2500/$\frac{125}{2}$–3000 and 2000–75–2425 + perks.

Scientists interested to serve the Institute may establish a contact with Joint Director, Institute of Medical Sciences, 51–52, Tulsi Bagh, Srinaga along with complete bio-data. The last date for receipt of application is 30th July, 1980.

Doctors who have already applied in response to our Preliminary Notice No. 21 dated 11–4–1979 need not apply again.

General information

Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available:

1.	PART I	(capitals)
2.	RESULTS	(small capitals)
3.	Blood-gas analysis	(l.c. roman)
4.	*The action of drugs*	(italics, centre)
5.	*Lung function studies*	(italics, full out)
6.	*Volume.* Large volumes. . . .	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet "Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors" (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

CORRESPONDENCE

It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

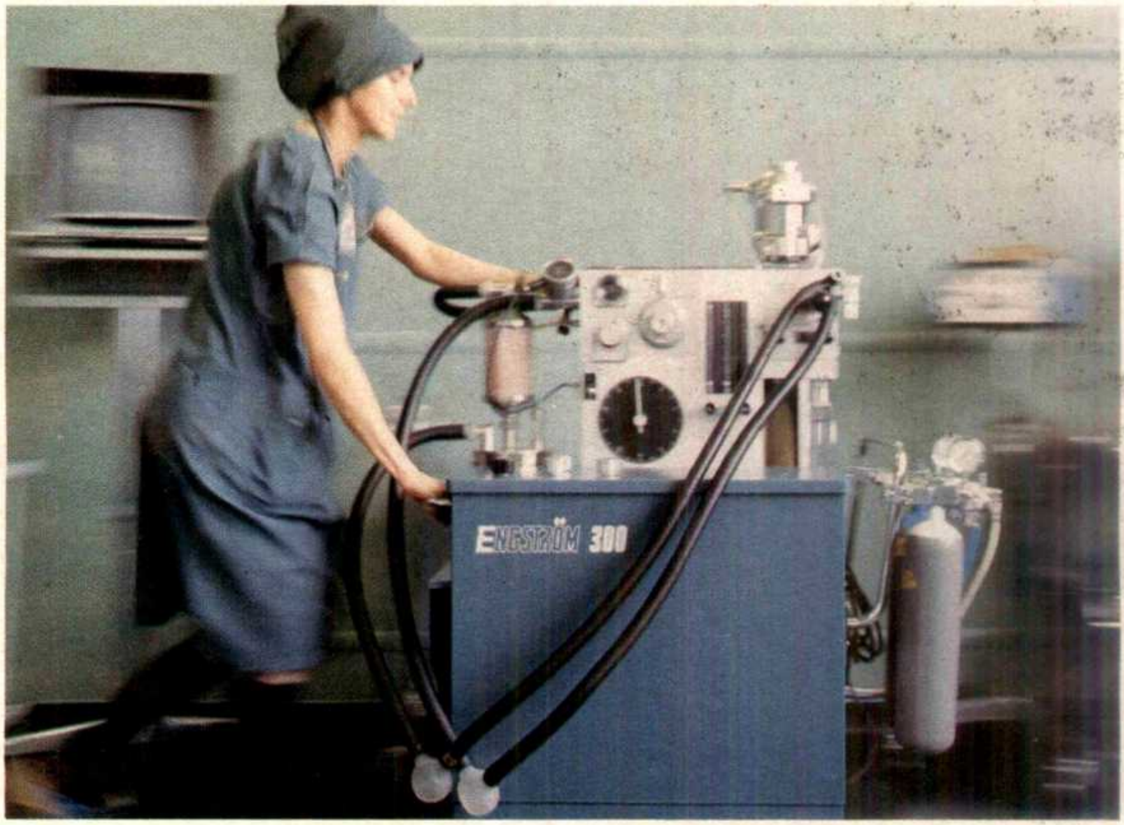
PROOFS

These should be corrected and returned to the sub-editor *within 48 hours of receipt.* Overseas contributors should return their proofs by airmail.

REPRINTS

Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

Just wheel it to where you need it.



Plug it into the mains, and it's ready to work.

The Engström 300 can operate as a completely self-contained unit. It can carry its own supplies of gas, and has its own built-in driving compressor.

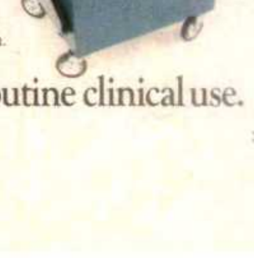
It is an all-purpose respirator. Models are available for both adults and children, and accessories make it easily adaptable for intensive care or anaesthesia.

Operation is simple. All settings are easy to make. The respirator automatically adapts to changes in the lungs of the patients.

All parts are designed to withstand much more than their share of hard use. Preventative maintenance and repair is done with simple tools.

These are some of the reasons why hospitals all over the world swear by their Engströms. We would like you to see for yourself. Contact your nearest Engström representative for more information, and you'll get our new brochure.

Or, if you would like to see it demonstrated on your own ground, he will arrange an appointment at your convenience.



ENGSTRÖM

Engström Medical AB,
Box 1295, S-171 25 Solna, Sweden.

Engström 300 - the self-contained, all-purpose respirator for routine clinical use.

Der Anaesthesist

The organ of the
Austrian, German and Swiss Societies
of Anaesthesiology and Reanimation

Edited by: A. Doenicke, München; R. Frey, Mainz; O. Mayrhofer, Wein; H. Schaer, Männedorf
Managing Editor: A. Doenicke, München, Chirurgische Universitäts-Poliklivik, Anaesthesie, Pettenkoferstr. 8a, D-8000, München 2

Contents DECEMBER 1979

U. Ottermann, R. Dudziak, E. Appel, D. Palm — The effect of hypothermia and methoxyflurane-anaesthesia on sympatho-neuronal and sympatho-adrenal activity in the course of cardiac surgery 551

K. Huse, H. Wiecken — Circulatory changes in the sitting position during neuorsurgical anaesthesia (NLA) 557

A. Csongrady, E. Mayr, H.-D. Kamp, H.-J. Volkholz — Dosage-Problems in controlled sodium nitroprusside hypotension in oto-rhino-laryngological surgery 564

S. Fitzal, E. Knapp-Groll, W. Ilias, W. Scherzer, L. Tonczar — A comparison of two preoperative medications: responses in sedative, psychic and somatic effects 572

A. Doenicke, J. Kugler, M. Kropp, M. Laub, G. Kalbfleisch — The hypnotic effect of the new benzodiazepine derivative lormetazepam when given introvenously 578

Th. Wallenfang, U. Mielke, J. Bohl, H. Bierbach — Local myocardial necrosis and cardiac tamponade due to a central venous catheter 584

Annual subscription: DM 180 + postage

Published by SPRINGER-VERLAG · Berlin · Heidelberg · New York

Anaesthetist required to replace retired Department Head. Active, well equipped Surgical Department in a progressive northern community. Six months in medical, surgical, obstetrics, and pediatrics required. Please contact:

Dr. Marjorie Papple,
Department of Anaesthesiology,
Mills Memorial Hospital,
4720 Haugland Avenue,
Terrace, British Columbia,
Canada. V8G 2W7.
Telephone: (604) 635-2211 or
(604) 635-5902.

Faculty Positions Open
COLLEGES OF MEDICINE
& MEDICAL SCIENCES

Department of Anaesthesia

KING FAISAL UNIVERSITY
DAMMAN, SAUDI ARABIA

TEACHING APPOINTMENTS

The expanding Colleges of Medicine & Medical Sciences invite applications for their Anaesthesia Department.

Candidates should have a minimum of 2 years teaching or practical experience.

Language of instruction is English.

Salaries are highly competitive and negotiable, comparable to other Saudi Arabian Universities.

BENEFITS:

Free furnished accommodation. Local transport allowance. Educational assistance for up to 4 children. Airfare to and from Saudi Arabia once a year for husband, wife and 2 children, plus a 60-day paid summer holiday.

Interviews will be held in the United Kingdom and the United States. Positions are available starting September 1980. Please send 3 copies of complete curriculum vitae and names, addresses and telephone numbers of 3 references to:-

Dr Tawfik Tamimi MD PhD
Dean, Colleges of Medicine &
Medical Sciences
King Faisal University

at the appropriate address below:-

PO Box 2, Sunbury-on-Thames
Middlesex TW16 5JP
England

c/o Saudi Arabian Educational Mission
2221 West Loop South
Houston, Texas 77027
USA

You've worked hard for your money

-now let it work hard for you.

Like you, we at Lombard rely on our hard earned skills. Our experience over many years has made us an important name in British Banking and Finance to help people like you make their money grow by depositing with us.

We have a wide range of specially designed Deposit Account Schemes offering sound rates of interest which is paid without deduction of tax at source.

For further details of our deposit facilities and current interest rates without any obligation, simply post the coupon today.

Lombard North Central
Bankers

To:
LOMBARD NORTH CENTRAL LTD.
DEPT. U942,
17 BRUTON STREET,
LONDON W1A 3DH.
Tel: 491 7050

Name:
(BLOCK CAPITALS PLEASE)
Address:

A member of the National Westminster Bank Group whose capital and reserves exceed £1,300,000,000.

XIIth INTERNATIONAL MEETING OF ANAESTHESIOLOGY AND RESUSCITATION

ANAESTHESIA AND POSTOPERATIVE CARE IN UNCOMMON DISEASES

VOLATILE HALOGENATED ANAESTHETICS

Paris, March 8–9, 1980

The meeting will be held at C.H.U. Pitié-Salpetrière.

Participants registering after February 15, 1980 will be subject to a fee surcharge of 500^F.

Registration forms available from, and all correspondence to:

J.E.P.U. Anesthésie Réanimation,
B.P. 386,
75626 Paris, Cédex 13,
France.

SUBSCRIBE TO ANAESTHESIA & INTENSIVE CARE

Published quarterly by the Australian Society of Anaesthetists. Subscription rate 1980 $Aust.28.00. ($US33.00, £Stg.15), back issues/individual copies $Aust.7.00 ($US8.50, £Stg.4.50).

Please send your subscription request to: ANAESTHESIA AND INTENSIVE CARE,
P.O. BOX 525, POTTS POINT, N.S.W. 2011, AUSTRALIA.

Name ______________________________

Address ______________________________

____

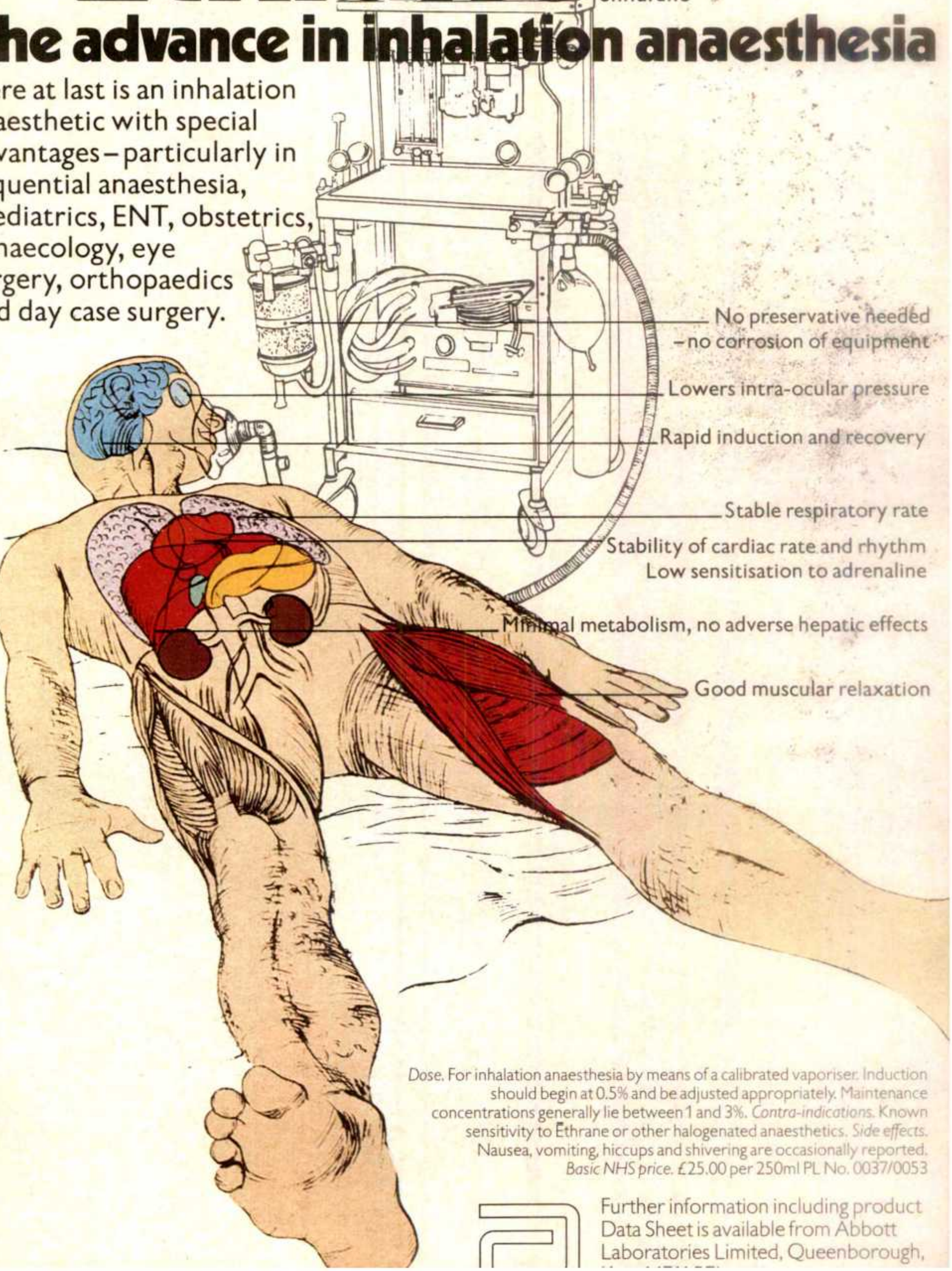
Country ____________________ Code ____________________

Send no money at this stage. We will invoice you and commence your subscription with the current issue.

Ethrane® enflurane

The advance in inhalation anaesthesia

Here at last is an inhalation anaesthetic with special advantages – particularly in sequential anaesthesia, paediatrics, ENT, obstetrics, gynaecology, eye surgery, orthopaedics and day case surgery.



No preservative needed – no corrosion of equipment

Lowers intra-ocular pressure

Rapid induction and recovery

Stable respiratory rate

Stability of cardiac rate and rhythm
Low sensitisation to adrenaline

Minimal metabolism, no adverse hepatic effects

Good muscular relaxation

Dose. For inhalation anaesthesia by means of a calibrated vaporiser. Induction should begin at 0.5% and be adjusted appropriately. Maintenance concentrations generally lie between 1 and 3%. *Contra-indications.* Known sensitivity to Ethrane or other halogenated anaesthetics. *Side effects.* Nausea, vomiting, hiccups and shivering are occasionally reported. *Basic NHS price.* £25.00 per 250ml PL No. 0037/0053

Further information including product Data Sheet is available from Abbott Laboratories Limited, Queenborough,

This Handbook is an essential reference for anaesthetists and those associated with the speciality.

Designed to provide factual and commercial information of value to departments of Anaesthesia in their dealings with other organisations and to those wishing to commence the practice of anaesthesia as a training.

Handbook of
British Anaesthesia
1979/80

Contents include comprehensive information on:
National and International bodies in Anaesthesia
National specialist societies
Regional and local societies
University departments of anaesthesia
National Health Service Postgraduate Training areas
and National Health Service Advisory and Consultative machinery

Published price of the Handbook is £5.95 but there is a special price to subscribers of the journal. For information write to:
Sally Pimley, Macmillan Journals Limited, 4 Little Essex Street, London WC2R 3LF, England.

September 14–21, 1980

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS 7th WORLD CONGRESS OF ANAESTHESIOLOGISTS HAMBURG

Federal Republic of Germany

Deadline for submission of abstracts: January 31, 1980

Deadline for registration: May 31, 1980

Further information by:

Organizing Committee
7th World Congress of Anaesthesiologists
c/o Hamburg Messe and Congress GmbH
—Dept. for Congress Organisation—
P.O. Box 30 23 60. D-2000 Hamburg 36
Federal Republic of Germany

INTENSIVE CARE SOCIETY

Council of the Intensive Care Society has awarded the 1979 Medishield Travelling Fellowship to Dr Charles J. Hinds of St Bartholomew's Hospital.

6TH ASIAN AND AUSTRALASIAN CONGRESS OF ANAESTHESIOLOGISTS

Auckland, New Zealand, January 19–22, 1982

Information can be obtained from:

The Convenor,
6th Asian and Australasian Congress of Anaesthesiologists
Department of Anaesthesia,
Auckland Public Hospital,
Auckland,
New Zealand.

The gentlest touch

The delicate tissue lining of the trachea needs the gentlest possible handling during intubation. That's why Searle have developed Sensiv, the ultra low pressure endotracheal tube:

- *Thin walled pre-formed cuff designed for unprecedented compliance*
- *Ultra low intracuff pressure remains below acceptable maximum even after long periods of anaesthesia*
- *No wrinkles formed on inflation—aspiration prevented.*

New **Sensiv**

Low pressure cuff endotracheal tube

Please return this coupon to:

Searle Medical Products,
Division of G. D. Searle & Co. Ltd.,
P.O. Box 88, Lane End Road,
High Wycombe, Bucks.

SEARLE

Please send me a sample and detailed information on Sensiv.

*Name*____________________

*Position*____________________

*Address*____________________

BA 9673A

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 2 FEBRUARY 1980

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement.

EDITORIAL

MUSCLE

Muscle makes up about 30% of the body mass. Its reflex activation in response to the pain accompanying trauma and surgery lead to one of the goals of anaesthesia. This activity can be abolished either by blocking the afferent limb of the reflex arcs by local anaesthetic techniques and perhaps by the actions of opiates on the early stages of the reflex network, by depression of the central nervous system by deep general anaesthesia or by blocking neuromuscular transmission by curare-like drugs.

Diseases of the muscle are not rare and anaesthetists may become involved in providing anaesthesia for them or in managing respiratory problems. Knowledge of the relevant physiology, biochemistry and pathology should enable a number of pitfalls to be avoided. Malignant hyperpyrexia is perhaps the most dramatic example of a situation in which the incorrect choice of anaesthetic technique may precipitate disaster and a proper choice avoid it. In this condition and in all muscle activity the regulation of the intracellular calcium concentration and its movements into and out of the various sub-cellular compartments is vital. Not all the problems are of academic interest only: the introduction of dantrolene, which can decrease the intracellular calcium ion activity, is of value in the early treatment of MH.

This issue of the Journal is devoted to reviewing some of the recent progress in understanding the physiology, biochemistry and pathology of muscle together with the anaesthetic problems of muscle disease. There are recent advances also in our understanding and use of neuromuscular blocking drugs and a review of these seems relevant to this issue.

F. R. Ellis
J. Norman

Br. J. Anaesth. (1980), **52,** 111

THE PHYSIOLOGY OF STRIATED MUSCLE

K. Floyd

The purpose of this article is to present current views on the physiology of striated muscle, and in particular on the mechanism of contraction and the way in which the contractile machinery is activated. The preparation which has been most extensively studied is the isolated living muscle fibre of the frog, and this fact has governed the choice of the experimental evidence cited. The plan of the article is to give a brief outline of structure, a description of the processes involved in activation, and an account of the development of ideas about the mechanism of contraction, starting from the sliding filament theory and A. F. Huxley's 1957 model.

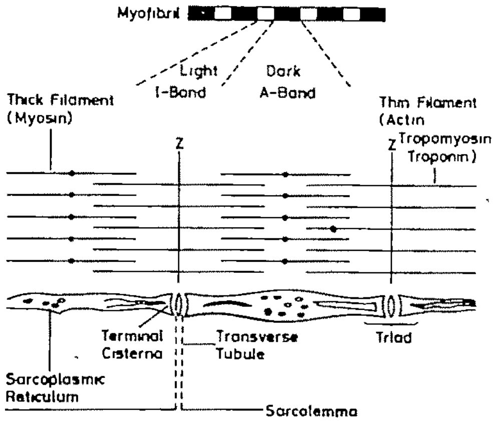


Fig. 1. Schematic diagram of the structure of frog skeletal muscle. Each muscle fibre (30–150 μm in diameter) is composed of a number of myofibrils (approx. 1 μm in diameter), and the light and dark bands in each myofibril are normally aligned to give each fibre its striped appearance. The thick filaments are about 1.6 μm in length and the thin filaments (including the Z-line) are between 1.95 and 2.0 μm in length. Structural details of the triads are illustrated in figure 2. Adapted from Ebashi, Endo and Ohtsuki (1969).

Structural outline. When viewed under a light microscope, a striated muscle fibre can be seen to consist of a number of myofibrils, each of which is made up of alternate light and dark bands. In an unstained or living fibre these bands, which result from materials of different refractive index, can be made visible by the use of polarized light or interference microscopy. It is now known that the dark or A-band consists of thick filaments of the protein myosin, while the light or I-band consists of thin filaments of the protein actin, together with the proteins tropomyosin and troponin which perform an important regulatory role. The main structural features are shown diagrammatically in figure 1.

In addition to the contractile proteins, striated muscle contains two internal membrane systems, the sarcoplasmic reticulum and the transverse tubules. The transverse tubules are invaginations of the surface membrane and run into the core of the muscle fibre. In contrast, the sarcoplasmic reticulum is composed of a longitudinal network of tubules which run into sacs or terminal cisternae where the sarcoplasmic reticulum comes into close proximity to the transverse tubules. The regions of conjunction appear as regularly spaced triads in longitudinal sections of muscle (a triad is a group of three "vesicles", consisting of a pair of terminal cisternae on either side of a transverse tubule). In frog muscle, triads are found at the level of the Z-line (fig. 2A), whereas in mammalian muscle they are situated at the level of the A–I boundary (fig. 2B).

ACTIVATION OF THE CONTRACTILE MECHANISM

Activation of vertebrate skeletal muscle is brought about by depolarization of the surface membrane, which results in the release of calcium ions from intracellular stores in the sarcoplasmic reticulum. The stages in this process will be summarized briefly and then described in more detail.

The action potential at the surface membrane is propagated radially into the core of the muscle fibre via the transverse tubular system. The depolarization of the transverse tubules results in the release of calcium ions from the adjacent terminal cisternae of the sarcoplasmic reticulum. The calcium ions diffuse into the interior of the myofibrils, where they

---

K. Floyd, B.Sc., M.Sc., Ph.D., Department of Physiology, Worsley Medical and Dental Building, University of Leeds, Leeds LS2 9NQ.

0007-0912/80/020111-11 $01.00

© Macmillan Journals Ltd 1980

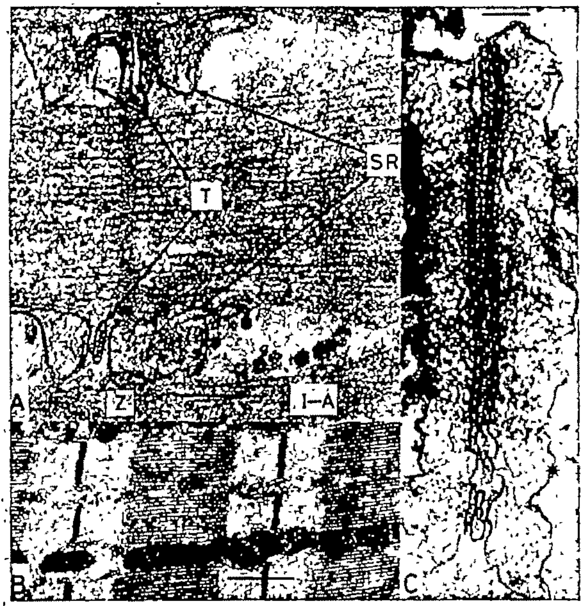


FIG. 2. (A): Frog (*Rana pipiens*) sartorius muscle in longitudinal section showing triads at the level of the Z-line (Z). I–A marks the ends of the thick filaments. Ferritin particles (which demonstrate continuity with the extracellular fluid) can be seen in the transverse tubules (T) but not in the sarcoplasmic reticulum (SR). Scale: 0.2 μm (derived from magnification given in original text). Peachey and Schild (1968) by permission of the *Journal of Physiology*. (B): Cat superior rectus muscle in longitudinal section showing triads at the level of the A–I boundary. Scale: 1 μm. Floyd (unpublished). (C) Frog (*Rana pipiens*) sartorius muscle in longitudinal section showing a single triad in tangent view. Note the periodically repeating feet, and a region (S) where the sarcoplasmic reticulum appears scalloped. The asterisk indicates an area of the sarcoplasmic reticulum where the contents appear particularly regular. Scale: 0.1 μm (derived from magnification given in original text). Franzini-Armstrong (1970) by permission of the Rockefeller University Press.

combine with the regulatory protein troponin. This removes an inhibitory influence exerted by tropomyosin on actin which can then interact with myosin to produce contraction of the muscle.

Excitation. Muscle fibres are electrically excitable cells similar in their essential features to nerve cells, and the first stage in activation normally involves an action potential which will arise when the potential difference across the cell membrane is reduced from its resting value of 90 mV (inside negative) to about 50 mV. Such a depolarization normally occurs at the motor endplate as a result of the arrival of an action potential at the motor nerve terminal, and the action potential generated in the muscle fibre membrane propagates in both directions to the ends of the fibre. It is the change in membrane potential itself which is the trigger to contraction, and the action potential at the surface membrane is followed by the sequence of events described previously.

If a muscle fibre is activated by direct depolarization in a solution containing a high concentration of potassium, a contracture occurs in which tension is produced for a few seconds, followed by spontaneous relaxation despite the fact that the membrane remains depolarized. Hodgkin and Horowicz (1960) found that the initial development of tension was related to membrane potential by a steep sigmoid curve with a threshold at about −50 mV. In addition, they showed that the restoration of the ability to contract after spontaneous relaxation required repolarization of the membrane for a certain period of time (repriming). Thus, both activation and repriming appear to be controlled by the membrane potential.

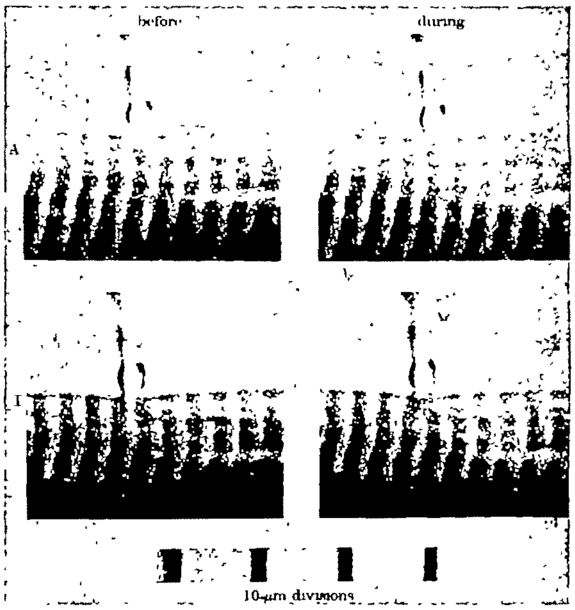


FIG. 3. Local activation of a twitch fibre from the semitendinosus muscle of *Rana temporaria*. Polarized light, compensated so that the A-bands appear dark. The fibre is immersed in, and the pipette is also filled with, Ringer's solution. Left-hand pictures before, and right-hand pictures during, an electric pulse applied to the pipette making the interior of its tip go roughly 100 mV negative relative to the surrounding fluid, for a period of about 0.5 s. In the upper pictures, the pipette is applied to an A-band, and there is no response. In the lower pictures, the pipette is applied to an I-band, and during the pulse that I-band (and only that I-band) shortens. Huxley and Taylor (1958), by permission of the *Journal of Physiology*.

Inward spread of activation. The existence of a specific inward-conducting mechanism located at the level of the Z-line in frog twitch fibres was elegantly demonstrated by Huxley and Taylor (1958) (fig. 3). The structure responsible for this inward spread of activation has since been shown to be the transverse tubular system. A full account of the association of inward spread of activation with the transverse tubules has been given by Huxley (1971).

The electrical conduction in the transverse tubules has been shown to be a regenerative process (Costantin, 1970, 1975) qualitatively similar to that in the surface membrane. In addition, it is now known that the action potential in the transverse tubules is necessary for normal contraction of frog muscle at 20 °C, but is less important at low temperatures (Bastian and Nakajima, 1974). The explanation for this is that at low temperatures the duration of the action potential is increased, and the prolonged depolarization of the surface membrane increases the effectiveness of purely passive spread of depolarization along the transverse tubules.

Coupling between transverse tubules and sarcoplasmic reticulum. The dependence of contracture tension on membrane potential has already been mentioned. If the action potential of an intact twitch fibre is blocked chemically, contractile activation can be produced by graded depolarization of the surface membrane, and contractile force is found to increase with the amplitude of membrane depolarization. Because the applied surface depolarization is attenuated along the transverse tubules under these circumstances, it is important to exclude the possibility that the observed increases in force are the result solely of progressive recruitment of more axially located myofibrils. Costantin and Taylor (1973) have shown that recruitment of myofibrils does occur with increasing depolarization, but they were also able to demonstrate a further gradation of force of contraction with increasing depolarization in contractions in which all myofibrils in the cross-section of the fibre were known to be activated. Thus, assuming that contractile force reflects the quantity of calcium released from the sarcoplasmic reticulum, the amount of calcium released during the activation process appears to be regulated by the transmembrane potential across the transverse tubules.

The membranes of the transverse tubules and sarcoplasmic reticulum are brought into close apposition in the triads by numerous small, electron-dense projections or "feet" of the terminal cisternae (fig. 2c), but there is believed to be no electrical continuity between the two membranes. How, then, does the depolarization of transverse tubules result in the release of calcium ions from the terminal cisternae?

In their quantitative description of the membrane currents in the squid giant axon, Hodgkin and Huxley (1952) suggested that the dependence of sodium and potassium conductance on membrane potential might arise from the effect of the electric field on the distribution or orientation of charged particles within the membrane. The charge movement within the membrane is accompanied by a membrane current (gating current) which is thought to reflect internal rearrangements.

Charge movements are detected in voltage clamp experiments on preparations in which ionic currents are abolished by channel-blocking agents and solutions of impermeant ions, and movement may be prevented by the use of hypertonic solutions. To illustrate the sort of procedures involved, it may be helpful to consider a particular experiment which investigates the idea that a charge movement associated with the voltage-dependent release of calcium may be reversed (remobilized) during the repriming period. The fibre was first depolarized to mobilize the "activation" charge; a comparison was then made between the membrane currents for two identical depolarizing voltage steps, one of which was preceded by a brief hyperpolarization, and the other by a repriming hyperpolarization which lasted for several seconds. The difference between the recorded currents thus detects the charge that is remobilized by the repriming hyperpolarization.

Adrian (1978) has discussed the difficulties of estimation and interpretation of charge movements in muscle fibre membranes, but he tentatively identifies charge movements related to the sodium channel, the potassium channel, and to contraction activation. However, the events which underlie the contraction activation charge movements are at present unknown, and the attractive idea that the charge movements directly regulate the release of calcium ions by affecting long molecules which interconnect the membranes of the two internal membrane systems via the "feet" of the terminal cisternae must remain speculative.

Changes in intracellular calcium concentration. It is now well established that contractile activation is achieved by the release of calcium ions from the sarcoplasmic reticulum. The presence of accumulations of calcium in the sarcoplasmic reticulum, and in the terminal cisternae, has been established by electron microscopy of preparations involving precipitation of calcium oxalate or autoradiography of calcium-45. Experiments on "skinned" muscle fibres, in which the surface membrane has been removed mechanically or chemically so that the bathing solution has direct access to the contractile proteins, have shown that the threshold concentration of calcium for initiating contraction is about 10^{-7} mol litre^{-1}, and maximum activation is obtained at 10^{-6} mol litre^{-1}. In the absence of calcium ions, the regulatory proteins, troponin and tropomyosin, exert an inhibitory effect on actin so that actin–myosin interaction is prevented. When calcium is released it binds to one of the troponin subunits, and the resulting changes in the conformation of the regulatory proteins remove the inhibition, enabling contraction to occur (Ebashi and Endo, 1968; Ebashi, Endo and Ohtsuki, 1969). Recent reviews by Sandow (1970), Fuchs (1974), Ebashi (1976), Endo (1977) and Caputo (1978) deal extensively with aspects of calcium release induced in skinned fibres, and this aspect will not be pursued further.

A rather different approach is to monitor changes in intracellular calcium concentration during normal contractions of living muscle. A promising advance in the measurement of changes in cytoplasmic calcium concentration has involved the intracellular injection of the calcium-sensitive bioluminescent protein aequorin, and results of such experiments in amphibian muscle have been reported by Blinks, Rüdel and Taylor (1978). They point out that limitations on the quantitative interpretation of the aequorin response at present preclude any conclusions about possible differences in the degree of activation in twitches and tetani. However, these limitations need not apply in circumstances where the geometrical relations among sites of calcium release, binding and sequestration are likely to be constant, such as during the series of twitches shown in figure 4, where changes in the aequorin response are believed to reflect changes in calcium release and uptake. Thus the decrease in light intensity reflects a progressive decrease in the amount of calcium released in successive twitches, and the simultaneous progressive slowing of decay of the aequorin response probably reflects a gradual slowing of the sequestration of calcium by the sarcoplasmic reticulum.

The influence of fibre length on luminescent and mechanical responses was also investigated by Blinks, Rüdel and Taylor (1978) who found that the aequorin response during tetani at 50 s^{-1} (15 °C) was maximal at sarcomere lengths of about 2.4 µm and decreased considerably at longer sarcomere lengths. A similar result was obtained from experiments on single twitches, except that the maximal aequorin responses in different fibres occurred at a range of sarcomere

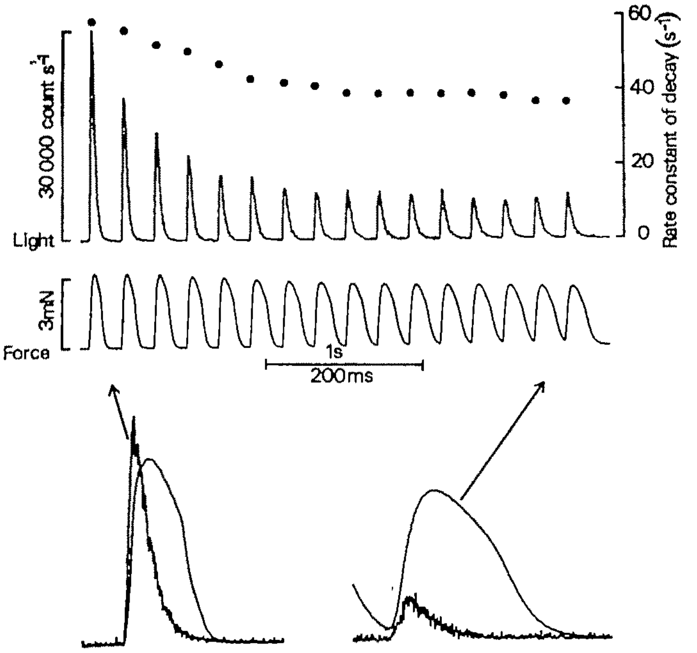


FIG. 4. Staircase phenomenon in successive isometric twitches. Single fibre from the tibialis anterior muscle of *Xenopus laevis*; striation spacing 2.1 µm; temperature 15 °C. Computer-averaged records of light (aequorin response) and force from 10 trains of 16 twitches during stimulation of the fibre at 5 s^{-1}. The lower panels show high-speed tracings of the first and last contractions in the series. The points above the light trace indicate rate constants for decay of aequorin luminescence in successive twitches. Blinks, Rüdel and Taylor (1978), by permission of the *Journal of Physiology*.

lengths from 2.4 to 3.0 μm. These results suggest that less calcium is released at long sarcomere lengths. The mechanism of this reduction of calcium release is unknown, but could be caused by reversible distortion of the junctional region between the transverse tubules and terminal cisternae.

The aequorin technique is obviously of major importance in the study of calcium transients in living fibres and improvements in precision of measurement and accuracy of localization are awaited with much interest. The implications of the results reported in the preceding paragraphs are far reaching. For example, measurements of the heat production associated with activation of muscle have assumed that the activation process was independent of length. Also, the changes in calcium concentration during repetitive stimulation suggest the need for a re-evaluation of the contribution of activation processes to maintenance heat (the steady production of heat during an isometric tetanus). These questions are considered, together with a detailed description of the steps that may contribute to the energetics of activation, in the reviews by Curtin and Woledge (1978) and Homsher and Kean (1978).

The lack of correlation between light output from aequorin and contractile force during the plateau of tetanic contractions could arise if the sarcoplasmic calcium concentration is greater than that required to saturate the regulatory proteins, thereby producing maximal activation of the contractile system. However, it is known that the maximum force generated in potassium contractures is appreciably greater than in tetani. Also, the maximum force developed by single fibres in tetani at optimum length can be increased by caffeine, nitrate or zinc ions, all of which apparently increase the tetanic aequorin response. It is to be hoped that these contradictions can be resolved soon.

THE CONTRACTILE RESPONSE

Mechanism of contraction

Length changes in striated muscle, whether active or passive, take place by a relative sliding motion between two sets of interdigitating filaments (fig. 1) which remain virtually unchanged in length. The sliding filament theory is now accepted as the structural basis of muscular contraction, but within its framework there are many possible mechanisms

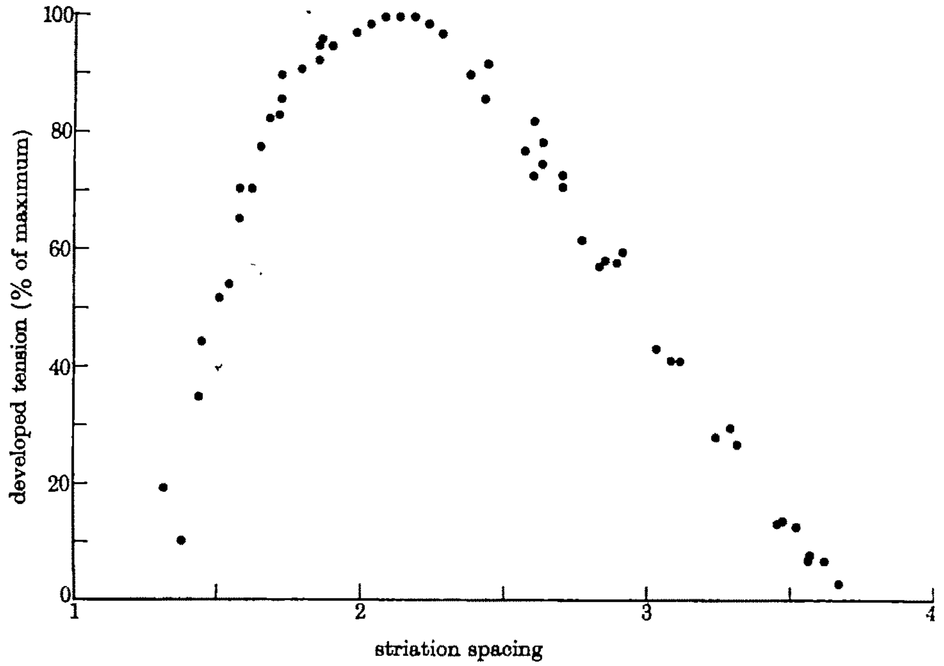


FIG. 5. Isometric tetanus tension developed by isolated fibres from the semitendinosus muscle of *Rana temporaria* at various lengths. Ordinate: tension increase above resting tension, as a percentage of the value in the plateau (2.05–2.20 μm). Abscissa: striation spacing (μm). Points compiled from the results of Gordon, Huxley and Julian (1966b). Huxley (1971), by permission of the Royal Society.

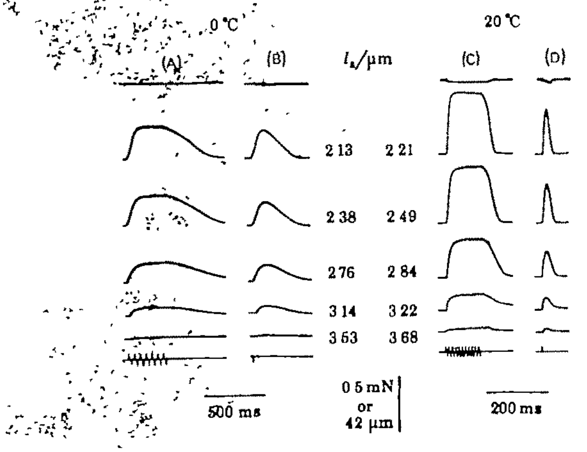


FIG. 6. Isometric tension developed by isolated single fibres from the tibialis anterior muscle of *Rana pipiens*. The top trace in each part is the output of the spot follower apparatus which indicates changes in marker separation (lengthening up) for the force records obtained at full overlap (2.13 μm and 2.21 μm; the corresponding marker separations were 1.85 mm and 1.90 mm respectively). At each sarcomere length (l_s) a twitch and a tetanus were recorded: in (A) tetani, and (B) twitches, the temperature was 0 °C; in (C) tetani, and (D) twitches, the temperature was 20 °C. The bottom trace is a record of the stimulus pattern. Julian, Sollins and Moss (1978), by permission of the Royal Society.

for the origin of the contractile force and some of these are discussed in the reviews by Huxley (1974) and Simmons and Jewell (1974).

The idea that a relative force between thick and thin filaments might be generated at each of a series of independent sites in the overlap zone was first put forward by Huxley and Niedergerke (1954). It follows that tetanic tension should be proportional to the number of sites at which tension is exerted on each thin filament and hence to the amount of overlap between thick and thin filaments. The determination of the isometric length–tension relation is complicated by non-uniformity in sarcomere length along a stretched fibre which arises because the ends do not elongate as much as the middle. A consequence of this is that during an isometric tetanus at long lengths the ends of the fibre shorten and stretch the middle part, causing a slow increase in tension. Gordon, Huxley and Julian (1966a, b) overcame this problem by using a photoelectric servo device to keep constant the length of a part of the isolated fibre within which the striation spacing was nearly uniform. The length–tension relation obtained (fig. 5) showed a linear decrease in tension at sarcomere lengths between 2.2 μm and 3.65 μm which corresponded closely with the region of overlap of the thin filaments with that part of the thick filament which carried projections. In experiments using isotonic tetani, with a microscope to measure sarcomere length and detect shortening, Huxley and Peachey (1961) found that there was no shortening when the striation spacing exceeded a critical value of 3.52 μm, which is reasonably close to the sarcomere length at which the thick and thin filaments no longer overlap.

The interpretation of tension records from fibres at stretched lengths, where tension may continue to increase slowly for several seconds, has been questioned by Ter Keurs, Iwazumi and Pollack (1978). They measured the steady tension reached after several seconds in contractions of stretched muscle fibres and found that this was not proportional to filament overlap at sarcomere lengths between 2.2 μm and 3.65 μm. This has led them to question the cross-bridge model of force generation. In contrast, Julian, Sollins and Moss (1978) (fig. 6) re-investigated the length–tension relation and have fully confirmed the proportionality of tension and filament overlap in stretched muscle fibres. The difference in results obtained is probably related to differences in the techniques and procedures used, but a satisfactory explanation has not yet been provided.

Another feature of contraction resulting from independent force generators is that the maximum speed of shortening (under zero external load) should be independent of the amount of overlap, provided there are no length-dependent internal forces

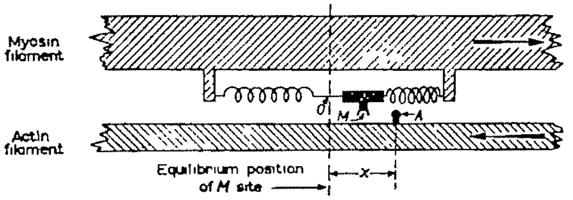


FIG. 7. A. F. Huxley's model of a thick filament projection. The parts of the filaments shown are in the right-hand half of an A-band, so that the actin filament is attached to a Z-line which is out of the picture to the right. The arrows give the direction of the relative motion between the filaments when the muscle shortens. The "side-piece" M, elastically connected to the thick filament, is assumed capable of binding to A sites (only one shown) on the thin filament. Attachment occurs spontaneously but may be reversible; detachment occurs principally by a process which involves the hydrolysis of an ATP molecule. Huxley (1957) by permission of Pergamon Press Ltd.

opposing shortening. Gordon, Huxley and Julian (1966b) found that the speed of active shortening under light loads did not change appreciably with the amount of overlap at striation spacings greater than 2 μm, and Edman (1979) has shown that velocity of shortening under zero load is approximately constant for sarcomere length between 1.7 and 2.7 μm.

A. F. Huxley's 1957 theory. A hypothesis for the mechanism of contraction was put forward by A. F. Huxley in 1957. Many of the details are probably incorrect, such as the structural features of the model, the method of force production and the chemical assumptions, but the mathematical treatment is independent of the original assumptions and represents a class of models based on the idea of cross-bridges as independent force generators. The general outline of the theory is that cross-bridges operate in a cycle consisting of attachment with moderate rate constant, exertion of force, and detachment with high rate constant after sliding motion of the filaments sufficient to bring the force near to zero. An essential feature is that the probabilities of attachment and detachment of the cross-bridges are determined by their position.

The essentials of the model are illustrated in figure 7. The contractile element shown is in the right-hand half of an A-band, so the actin filament is attached to a Z-line which is out of the picture to the right. During shortening, therefore, the actin filament moves to the left relative to the myosin filament. The distance of A, the active site on the thin filament, from 0, the equilibrium position of the M site on the thick filament, is denoted by x (which is positive when A is to the right of 0). The "side-piece" M oscillates over a range of ± 10 nm about its equilibrium position 0 as a result of thermal agitation. If an A site happens to be within range there is a chance that attachment of M with A may occur, but in order to provide directionality the combination can occur only to the right of 0 (x positive) so that the tension in the elastic element is in the direction to cause the muscle to shorten. The AM combination moves towards 0 as the muscle shortens; there is a small chance that the link will be broken, but the probability increases greatly when the AM link passes 0 (and x becomes negative) and detachment occurs, thereby preventing the tension in the elastic link (which has now become negative—a force tending to extend the muscle) from hindering the shortening of the muscle. At high rates of shortening a large proportion of the links will not be broken in time to prevent a considerable resistance being developed in this way; the speed of shortening of an unloaded muscle reaches its limit when this resistance just equals the force produced by the links to the right of 0. Because the maximum velocity of shortening depends on the balance of these forces, but not on their magnitude, it follows that maximum velocity should be independent of the number of sites that are active and should therefore be independent of the degree of activation of the muscle. Edman (1979) has presented data from experiments on single muscle fibres which show that the velocity of shortening under zero load is unaffected by conditions which substantially alter contractile force and thus strongly support the idea that maximum shortening velocity is independent of the number of myosin bridges that are able to interact with the thin filament.

The absolute value of maximum velocity of shortening depends mainly on the value chosen for the rate of detachment during shortening; a high value reduces the proportion of attached bridges which can reach large negative values of x and consequently a higher shortening velocity can occur before the net force decreases to zero. The magnitude of the value of the rate of attachment mainly influences the number of bridges attached and in consequence affects the shape of the force–velocity relations (Simmons and Jewell, 1974).

In his mathematical development of the theory, Huxley chose values for the rates of attachment and detachment which gave the best fit with the mechanical and energetic data then available (Hill, 1938). Mention has already been made of the need for further investigation of activation and maintenance heat (Curtin and Woledge, 1978; Homsher and Kean, 1978). In addition, the report by Allen (1978) that aequorin light emission decreases during shortening indicates a change in some facet of the activation process which has not yet been included in evaluation of the energetic cost of shortening.

Another group of experimental findings which are not accounted for by the 1957 theory are the "transient" responses that can be observed when either the load on a muscle fibre or its length is suddenly changed. In this type of experiment, when a sudden small reduction of length is imposed during an isometric contraction, the ensuing tension changes show four phases (fig. 8): (1) an instantaneous decrease of tension, (2) an early tension recovery which lasts only a few milliseconds, (3) a reduction or reversal of the rate of tension recovery, and (4) a gradual recovery of tension with asymptotic approach to the isometric tension. Phase (4) resembles the final part of the increase in tension at the start of the tetanus and the

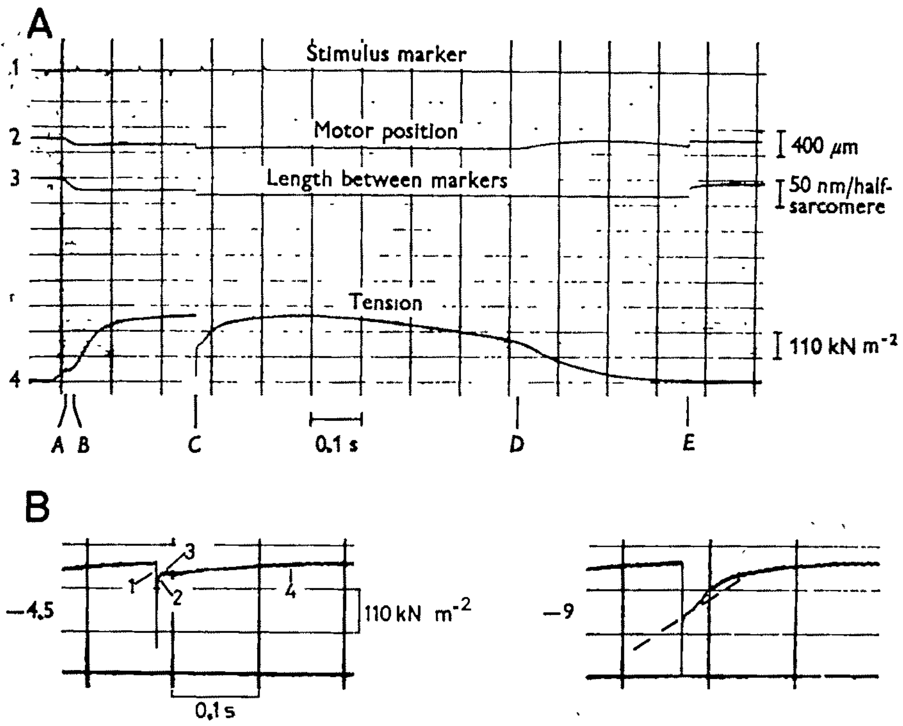


FIG. 8. (A): U.v. record to show the sequence of events during a contraction. Initially the servo is controlled from the motor-position signal. At A, tension reaches a preset value, and is then held at that value by the servo so that the fibre shortens isotonically until B, when the sarcomere length reaches its preset value. The servo now holds sarcomere length constant at this value, and the contraction is truly isometric until E, apart from the shortening step (9 nm per half sarcomere) imposed at C, and local elongation during relaxation at D. The servo is permitted to return to tension control at E. Sarcomere length 2.2 µm; temperature 1.0 °C. (B): U.v. records of tension during tetani with step reduction of length of 4.5 nm and 9 nm per half-sarcomere. Same experiment as (A). The four phases of the tension transient are marked on the left-hand trace. The broken line on the 9-nm record is the tangent to the tension trace at the point of inflexion during phase (3); its intersection with the initial decrease of tension is taken as T_2 (see fig. 9). Compiled from Ford, Huxley and Simmons (1977), by permission of the *Journal of Physiology*.

predominant process is presumably attachment of cross-bridges at the new fibre length. Phase (3) could be accounted for by a predominance of detachment over attachment, but this requires a modification to the 1957 theory in respect of the way in which the probabilities of attachment and detachment vary with the position of the cross-bridge (Huxley and Simmons, 1973).

The early events which constitute phases (1) and (2) of the tension transients are shown in figure 9. In the tension trace there is an initial step at the time of the imposed length change, after which the tension recovers, in a few milliseconds, part of the way towards the isometric value. The relations between the length change and tension for a series of steps of different amplitude are also shown in figure 9. The curve T_1/T_0 shows the extreme tension reached during the step change in length, and is a measure of the instantaneous stiffness of the fibre. The upward concavity is largely a result of the rapid onset of the early tension recovery, so the true intercept is probably between −4 and −5 nm, and the relation practically linear. In contrast, the early tension recovery, T_2/T_0 is highly non-linear; recovery is almost complete in releases (and stretches) in which the length change is only a few nanometres, but becomes progressively less complete in the larger releases so that the curve is concave downwards with a slope somewhat less than that of the T_1/T_0 curve. This suggests that the structures responsible for the tension recovery are

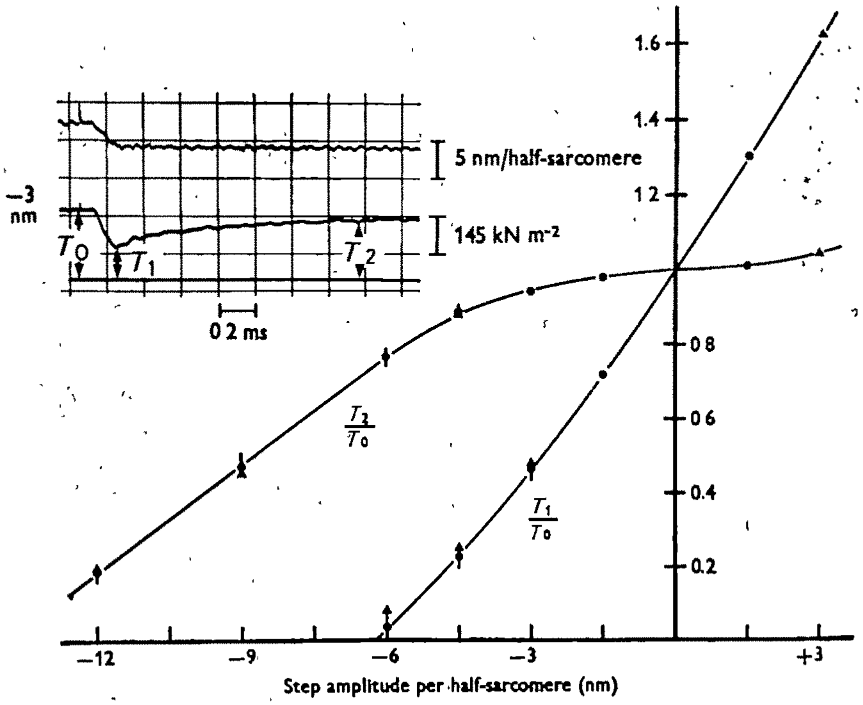


FIG. 9. Curves of T_1 (extreme tension) and T_2 (tension approached during early recovery phase) in length-controlled steps of various amplitudes, both expressed as fractions of T_0, the isometric tension immediately before the step. Circles and vertical lines refer to means and ranges respectively of four series of records from one fibre; triangles are the fourth run in the series from records shown in figure 12 of the paper. Sarcomere length 2.2 μm; temperature 2.5 °C. Inset shows the initial change in tension on a fast time-base for a −3-nm length change in the same fibre, and has been labelled to indicate T_0, T_1 and T_2. Compiled from Ford, Huxley and Simmons (1977), by permission of the *Journal of Physiology*.

not just passive visco–elastic elements but are the tension generators themselves, that is the cross-bridges. The displacement of the main part of the T_2/T_0 curve some 6 nm to the left of the T_1/T_0 curve suggests that some "active" part of the cross-bridge can take up approximately 6 nm of shortening while maintaining a tension not much less than it exerts in an isometric contraction.

An important point in the development of a new theory was the discovery that, at different sarcomere lengths, the size of the responses to a given size of step varied in direct proportion to the isometric tension, and hence to the amount of overlap. Thus the instantaneous elasticity, as well as the early recovery, is attributable to the cross-bridges.

Another non-linearity in the early tension recovery is the fact that its time course varies with the direction and amplitude of the length step, being slowest in a large stretch, fastest in a large release, and varying continuously in between.

A. F. Huxley and Simmons' 1971 theory. The general outline of the theory is that attached cross-bridges can exist in a small number of stable positions and that the tension in the bridge influences the probability of it being in a particular position. The essentials of the scheme are illustrated in figure 10, which is framed in terms of the "tilting head" cross-bridge model of H. E. Huxley (1969), although there are many other structural possibilities, some of which are outlined by A. F. Huxley (1974). In the model the stable positions are those where a pair of sites is combined. During shortening the head attaches, rotates clockwise into successive stable positions and detaches when it has reached the last position. Clockwise rotation into successive positions occurs because the stable positions have progressively less potential energy, whereas tension in the elastic element tends to cause backward movement. In response to a step reduction in fibre length, the tension in the elastic element is reduced and this increases the tendency

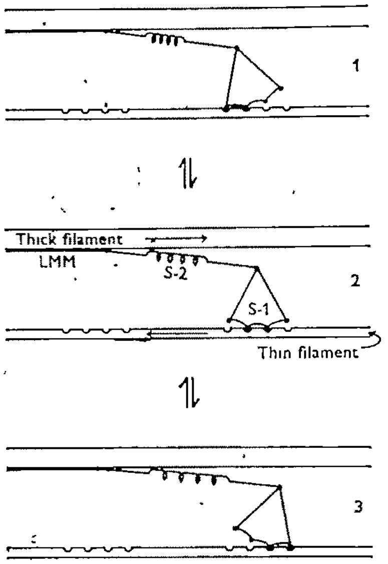


FIG. 10. Huxley and Simmons' (1971) version of the "tilting head" cross-bridge model to incorporate the elastic and stepwise-shortening elements inferred from the experiments on tension transients. The strength of binding of the attached sites is greater in position 2 than position 1, and in position 3 than position 2. During isometric contraction the myosin head oscillates rapidly between its three stable positions. The myosin head can be detached from position 3 with the utilization of a molecule of ATP; this is the predominant process during shortening. During stretch, the myosin head can dissociate from position 1 without utilization of ATP. Huxley (1974), by permission of the *Journal of Physiology*.

of the head to rotate clockwise. The larger the shortening step, the less the tension in each elastic element and the greater the tendency to rotate. This movement therefore occurs more rapidly, and shows itself in the experimental records as the fast time course of early recovery following a large release. This explanation of the early tension recovery is strengthened by the observations of Ford, Huxley and Simmons (1974) that the instantaneous stiffness is slightly decreased towards the end of the early tension recovery. Thus the early tension recovery takes place without an increase in the number of attached cross-bridges.

Relaxation

When stimulation ceases during an isometric tetanus the tension remains constant for a brief period, starts to decline slowly and then decreases exponentially to the baseline. At the end of the slow decline, the tension "shoulder" is accompanied by a rapid lengthening of part of the fibre. The converse of this observation can be seen in figure 8 where the "spot-follower" device was being used to hold the middle part of the fibre at constant length: the onset of the rapid exponential phase has been considerably delayed. In the 1957 theory the value for the rate at which the attached side-pieces turn over during isometric contraction was derived from the rate constant of the late exponential decrease in tension, but there is no longer any basis for this because substantial internal length changes are occurring at the time tension is decreasing exponentially (Huxley and Simmons, 1973).

The removal of free calcium from the sarcoplasm is believed to occur by means of the sarcoplasmic reticulum calcium pump. However, the active accumulation of calcium by the sarcoplasmic reticulum in isolated vesicles and skinned fibres appears to be somewhat less than is required to account for relaxation (Endo, 1977). The functional roles of calsequestrin and high-affinity calcium-binding protein are not yet well established, and the role of parvalbumin, a calcium-binding protein in the sarcoplasm, is unknown (Endo, 1977; Curtin and Woledge, 1978; Tada, Yamamoto and Tonomura, 1978). The remaining stages in relaxation are switching on the inhibition of actin by the troponin–tropomyosin complex and the detachment of cross-bridges, the latter being the direct cause, but not necessarily the rate-limiting step, of the decrease in isometric tension.

ACKNOWLEDGEMENT

I am indebted to Professor B. R. Jewell for many helpful suggestions on the manuscript.

REFERENCES

Adrian, R. H. (1978). Charge movement in the membrane of striated muscle. *Ann. Rev. Biophys. Bioeng.*, **7**, 85.

Allen, D. G. (1978). Shortening of tetanized skeletal muscle causes a fall of intracellular calcium concentration. *J. Physiol. (Lond.)*, **275**, 63P.

Bastian, J., and Nakajima, S. (1974). Action potential in the transverse tubules and its role in the activation of skeletal muscle. *J. Gen. Physiol.*, **63**, 257.

Blinks, J. R., Rüdel, R., and Taylor, S. R. (1978). Calcium transients in isolated amphibian skeletal muscle fibres: detection with aequorin. *J. Physiol. (Lond.)*, **277**, 291.

Caputo, C. (1978). Excitation and contraction processes in muscle. *Ann. Rev. Biophys. Bioeng.*, **7**, 63.

Costantin, L. L. (1970). The role of sodium current in the radial spread of contraction in frog muscle fibres. *J. Gen. Physiol.*, **55**, 703.

Costantin, L. L. (1975). Contractile activation in skeletal muscle. *Prog. Biophys. Molec. Biol.*, **29**, 199.

—— Taylor, S. R. (1973). Graded activation in frog muscle fibres. *J. Gen. Physiol.*, **61**, 424.

Curtin, N. A., and Woledge, R. C. (1978). Energy changes and muscular contraction. *Physiol. Rev.*, **58**, 690.

Ebashi, S. (1976). Excitation–contraction coupling. *Ann. Rev. Physiol.*, **38**, 293.

—— Endo, M. (1968). Calcium ion and muscle contraction. *Prog. Biophys. Molec. Biol.*, **18**, 123.

—— —— Ohtsuki, I. (1969). Control of muscle contraction. *Q. Rev. Biophys.*, **2**, 351.

Edman, K. A. P. (1979). The velocity of unloaded shortening and its relation to sarcomere length and isometric force in vertebrate muscle fibres. *J. Physiol. (Lond.)*, **291**, 143.

Endo, M. (1977). Calcium release from the sarcoplasmic reticulum. *Physiol. Rev.*, **57**, 71.

Ford, L. E., Huxley, A. F., and Simmons, R. M. (1974). Mechanism of early tension recovery after a quick release in tetanized fibres. *J. Physiol. (Lond.)*, **240**, 42P.

—— —— —— (1977). Tension responses to sudden length change in stimulated frog muscle fibres near slack length. *J. Physiol. (Lond.)*, **269**, 441.

Franzini-Armstrong, C. (1970). Studies of the triad. I: Structure of the junction in frog twitch fibres. *J. Cell. Biol.*, **47**, 488.

Fuchs, F. (1974). Stirated muscle. *Ann. Rev. Physiol.*, **36**, 461.

Gordon, A. M., Huxley, A. F., and Julian, F. J. (1966a). Tension development in highly stretched vertebrate muscle fibres. *J. Physiol. (Lond.)*, **184**, 143.

—— —— —— (1966b). The variation in isometric tension with sarcomere length in vertebrate muscle fibres. *J. Physiol. (Lond.)*, **184**, 170.

Hill, A. V. (1938). The heat of shortening and the dynamic constants of muscle. *Proc. R. Soc.* B, **126**, 136.

Hodgkin, A. L., and Horowicz, P. (1960) Potassium contractures in single muscle fibres. *J. Physiol. (Lond.)*, **153**, 386.

—— Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (Lond.)*, **117**, 500.

Homsher, E., and Kean, C. J. (1978). Skeletal muscle energetics and metabolism. *Ann. Rev. Physiol.*, **40**, 93.

Huxley, A. F. (1957). Muscle structure and theories of contraction. *Prog. Biophys. Biophys. Chem.*, **7**, 255.

—— (1971). The activation of striated muscle and its mechanical response. *Proc. R. Soc.* B, **178**, 1.

—— (1974). Muscular contraction (Review Lecture). *J. Physiol. (Lond.)*, **243**, 1.

—— Niedergerke, R. (1954). Interference microscopy of living muscle fibres. *Nature (Lond.)*, **173**, 971.

—— Peachey, L. D. (1961). The maximum length for contraction in vertebrate striated muscle. *J. Physiol. (Lond.)*, **156**, 150.

—— Simmons, R. M. (1971). Proposed mechanism of force generation in striated muscle. *Nature (Lond.)*, **233**, 533.

—— —— (1973). Mechanical transients and the origin of muscular force. *Cold Spring Harb. Symp. Quant. Biol.*, **37**, 669.

—— Taylor, R. E. (1958). Local activation of striated muscle fibres. *J. Physiol. (Lond.)*, **144**, 426.

Huxley, H. E. (1969). The mechanism of muscular contraction. *Science, N.Y.*, **164**, 1356.

Julian, F. J., Sollins, M. R., and Moss, R. L. (1978). Sarcomere length non-uniformity in relation to tetanic responses of stretched skeletal muscle fibres. *Proc. R. Soc.* B, **200**, 109.

Peachey, L. D., and Schild, R. F. (1968). The distribution of the T-system along the sarcomeres of frog and toad sartorius muscles. *J. Physiol. (Lond.)*, **194**, 249.

Sandow, A. (1970). Skeletal muscle. *Ann. Rev. Physiol.*, **32**, 87.

Simmons, R. M., and Jewell, B. R. (1974). Mechanics and models of muscular contraction; in *Recent Advances in Physiology* (ed. R. J. Linden), p. 87. Edinburgh: Churchill Livingstone.

Tada, M., Yamamoto, T., and Tonomura, Y. (1978). Molecular mechanism of active calcium transport by sarcoplasmic reticulum. *Physiol. Rev.*, **58**, 1.

Ter Keurs, H. E. D. J., Iwazumi, T., and Pollack, G. H. (1978). The sarcomere length–tension relation in skeletal muscle. *J. Gen. Physiol.*, **72**, 565.

Br. J. Anaesth. (1980), **52**, 123

MUSCLE BIOCHEMISTRY

J. A. ILLINGWORTH

Our understanding of muscle biochemistry has improved considerably in recent years, not only in terms of the molecular details of the contraction mechanism, but also as a result of a growing awareness of the biochemical differences between the various muscle fibre types. Histological differentiation is increasingly seen to reflect an exquisite degree of biochemical specialization to fit each muscle for its particular physiological role. Quite apart from its aesthetic appeal, this situation has considerable practical importance, since it is this same biochemical specialization which permits selective drug action to be confined to a particular muscle type, and offers the possibility of further pharmacological advances in the foreseeable future.

The contraction mechanism itself has been extensively reviewed in recent years (Huxley, 1972; Weber and Murray, 1973; Ebashi, 1974; Perry, 1975, 1979; Mannherz and Goody, 1976) and only the briefest account will be given here in order to provide a basis for the subsequent discussion of comparative muscle biochemistry. In striated muscle contractions are normally associated with depolarization of the plasma membrane, which initiates the release of calcium ions from intracellular stores within the sarcoplasmic reticulum. These calcium ions bind to troponin C, a regulatory protein associated with the thin filaments, producing a change in protein conformation. This shape change is transmitted to the other thin filament components (troponin T, troponin I, tropomyosin and actin) with the eventual result that the actin subunits within the thin filaments are permitted to interact with the neighbouring myosin molecules in the thick filaments. Cross-bridge formation then commences, and the thin and thick filaments begin to slide relative to one another, powered by ATP hydrolysis, which is catalysed by the ATPase activity resident within the myosin molecule. The contraction ceases when the calcium ions are re-accumulated by the sarcoplasmic reticulum through the operation of an ATP-driven pump, commonly known as the Ca^{2+} ATPase.

FIBRE TYPES

The basic contraction mechanism outlined above is considerably modified in smooth muscle, while even among striated muscles there exist numerous refinements to satisfy the differing physiological functions of the various fibre types. At this writing it is possible for biochemists to distinguish readily three basic types of voluntary skeletal muscle fibre: slow twitch oxidative, fast twitch oxidative–glycolytic and fast twitch glycolytic (Peter et al., 1972; Hooker and Baldwin, 1979), corresponding to the neuropathologists' classifications 1, 2A and 2B respectively (Dubowitz and Brooke, 1973). The biochemistry of cardiac muscle is quite obviously distinct from any of the skeletal muscle fibre types, and it is increasingly practicable to distinguish between visceral and vascular smooth muscle, with the possibility of further refinement in the future.

Type 1 fibres have low contraction speeds, low glycolytic capacities and are rich in mitochondria and myoglobin. They have a red appearance and are adapted for steady, continuous work output without fatigue, operating with a largely fat-based metabolism.

Type 2A fibres combine high contraction speeds with an abundance of mitochondria and a high glycolytic capacity. They also have a red colour as a result of their high myoglobin content, and a good resistance to fatigue.

Type 2B fibres have high contraction speeds and a high glycolytic capacity, but are low in mitochondria and myoglobin, leading to a pale appearance and a low resistance to fatigue. They have a relatively poor capillary blood supply, and rely mainly on stored glycogen for energy production, although their maximal work output may be very high for short periods. Lactate accumulates extensively within these large-diameter fibres when the muscle is worked to exhaustion.

In contrast to this, the two oxidative fibre types both have a well-developed vascular supply and a much narrower diameter, as is necessary for the efficient exchange of gases and nutrients across the plasma membrane. Under normal physiological conditions there is very little lactate production

---

JOHN A. ILLINGWORTH, Department of Biochemistry, University of Leeds, 9 Hyde Terrace, Leeds LS2 9LS.

0007-0912/80/020123-16 $01.00

© Macmillan Journals Ltd 1980

within these oxidative muscles, which can, if necessary, utilize exogenous lactate as a source of energy. Oxidative and non-oxidative muscles differ in their lactate dehydrogenase isoenzyme content (Kaplan and Goodfriend, 1964), but there is no totally convincing explanation for this observation at present.

It should, of course, be emphasized that any normal skeletal muscle contains all three fibre types, although one or other may predominate in certain muscles. Physical training can lead to alterations in muscle enzyme concentrations (Holloszy and Booth, 1976), but the fibre-type ratios remain constant. Both types of red fibre contract effectively at light loadings, while the type 2B fibres are only recruited when a maximal effort is demanded. All of the fibres activated by a given motor neurone exhibit very similar biochemical features, and it is now known from cross-innervation experiments that slow fibres can be transformed into fast fibres, and *vice versa*, by subjecting them to the appropriate stimulation regime. These changes require alterations in the pattern of gene expression within the muscle fibres, and involve the synthesis of new contractile proteins and new enzymes responsible for energy-yielding metabolism (Pette and Dolken, 1974; Amphlett et al., 1975; Weeds and Burridge, 1975; Pette and Schnez, 1977; Roy et al., 1979). It is clear from the results of direct electrical stimulation experiments that these changes are primarily a response to stimulation frequency, and that no neurohumoural factor is apparently necessary.

Cardiac muscle most closely resembles type 1 skeletal muscle in its very slow contraction speed and strictly oxidative metabolism heavily biased towards the breakdown of fats rather than carbohydrates. Roughly 30% of the cell volume in heart is occupied by mitochondria, which have well-developed cristal membranes, and a high content of oxidative enzymes. The tissue is rich in myoglobin, and has an extensive vascular supply.

As might be expected, muscles with high contraction speeds tend to have an extensively developed sarcoplasmic reticulum, as is obviously necessary for the rapid uptake and release of calcium ions. The sarcoplasmic reticulum becomes progressively less important in type 1, cardiac and smooth muscles as befits their progressively slower twitch speeds. In cardiac muscle and smooth muscle there have been repeated suggestions of a mitochondrial involvement in calcium sequestration (Carafoli and Crompton, 1978; Crompton et al., 1978), but the majority view remains sceptical of this hypothesis at present. Prolonged electrical stimulation of fast-twitch fibres causes the sarcoplasmic reticulum to re-differentiate, with properties resembling those found in a slow-twitch fibre (Heilmann and Pette, 1979). These changes precede the eventual alterations in myosin isoenzyme pattern (see below) and involve a reduced rate of calcium transport, together with the synthesis of novel polypeptide components. The reaction mechanism of the Ca^{2+} ATPase itself appears to be rather similar in the various fibre types, and has been recently reviewed by Tada, Yamamoto and Tonomura (1978) and by DeMeis and Vianna (1979).

CONTRACTILE APPARATUS

Differences in physiological function are also reflected in the detailed architecture of the myofilaments, which can now be discussed more fully. As is illustrated in figure 1, each thin filament consists of a helical polymer containing many hundreds of individual actin subunits, each with a molecular weight of 40 000 daltons. Throughout the length of the thin filament the actin subunits are grouped into blocks of seven by molecules of tropomyosin, and this is reflected in the simple molar ratios between the major muscle components (Potter, 1974). Tropomyosin is a long, thin molecule of 68 000 daltons containing two subunits. The amino acid sequence of tropomyosin is repetitious (Stone and Smillie, 1978), suggesting that the present 14 actin binding sites have evolved through the repeated duplication of a shorter, primordial tropomyosin gene. It seems likely that the behaviour of the actin molecules within each septet is in some way co-ordinated by the tropomyosin, although the functional details remain obscure at present.

The actin isoenzymes found in differentiating myoblasts and non-muscle cells are distinct from the major form in mature muscle (Clarke and Spudich, 1977), although the differences between the various muscle fibre types seem to be relatively minor. There are, however, two distinct tropomyosin genes coding for α- and β-type subunits, and the subunit ratios have been found to vary in different muscle types (Cummins and Perry, 1974). There is at present no obvious correlation between tropomyosin isoenzymes and contraction speed, so the selective advantages offered by the arrangement remain a mystery.

Each tropomyosin molecule is also linked through a molecule of troponin T to the calcium-binding protein, troponin C, which is in turn linked back to an actin molecule via the third type of troponin subunit, troponin I. These protein–protein interactions seem

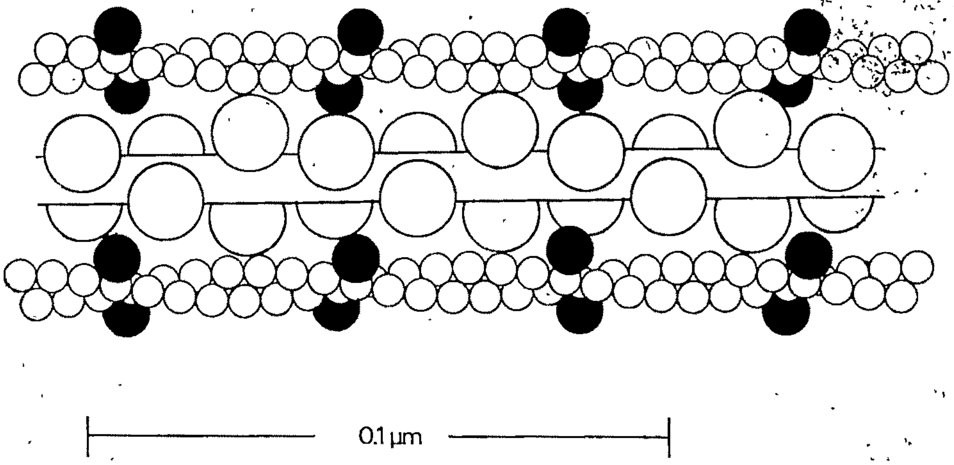


FIG. 1. Repeating patterns within striated muscle filaments. A single thick filament is shown, between two thin filaments. The myosin head groups (large open circles) are arranged in a helical pattern on the surface of the thick filament, with the long myosin tails aligned along the filament axis. The actin subunits (small open circles) are also disposed in a helical fashion to form the backbone of the thin filaments. Troponin complexes (filled circles) are spaced along the thin filaments at every seventh actin subunit. Tropomyosin dimers (which have been omitted for clarity) lie along the axis of the thin filaments, in the grooves between the actin monomers, and link each block of seven actin subunits to their controlling troponin complex. It will be noted that the periodicity of the thick filament helix differs slightly from that of the thin filaments, although the reason for this remains a matter of speculation.

to be extremely tenacious, and allow the shape changes associated with calcium binding to troponin C to be transmitted to the neighbouring actin subunits. (It should be noted that the three troponin components are named for their functions, *viz.* troponin T (36 000 daltons) for tropomyosin binding, troponin C (18 000 daltons) for calcium binding, troponin I (23 000 daltons) for its inhibition of purified actomyosin ATPase in the absence of the other components.) Distinct isoenzymes of troponin I are present in fast skeletal, slow skeletal and cardiac muscle (Dhoot and Perry, 1979). Cardiac troponin C (Head, Weeks and Perry, 1977) and cardiac troponin T (Tsukui and Ebashi, 1973) are different from the fast skeletal muscle isoenzymes, although the possible distinctions between fast and slow skeletal muscle remain to be resolved. Although the functional basis for most of this specialization remains obscure, some of the advantages offered by the unique cardiac troponin I are now becoming clear. This molecule has an extended N-terminal amino acid sequence, containing a serine residue which can be phosphorylated by cyclic AMP-dependent protein kinase to yield a phosphoprotein in which the adjacent troponin C subunit has a reduced affinity for calcium ions (Ray and England, 1976; Moir and Perry, 1977; Bailin, 1979). It is now thought that this permits relaxation at a higher free [Ca^{2+}] in adrenaline-stimulated cardiac muscle, thereby facilitating the well-known chronotropic effects of catecholamines in this organ.

It should be emphasized that this form of regulation by covalent modification of a pre-existing protein has proved to be exceedingly common in all types of living organism, and the past few years have seen a rapid increase in our understanding of this type of system. Dozens of examples have now been catalogued (Krebs and Beavo, 1979), and in mammalian species the vast majority have proved to involve a protein kinase-catalysed phosphorylation of the protein using ATP, followed by the eventual removal of the phosphate catalysed by a specific protein phosphatase. The complete cycle may be repeated many thousands of times during the life of a single protein molecule, according to the varying physiological needs of the animal. The phospho and dephospho forms of each protein usually differ considerably in biological activity, and it will be seen that this type of arrangement is at the same time more economical than the synthesis of a fresh protein when circumstances change, and yet more permanent than the use of a low molecular weight effector for the allosteric regulation of enzyme activity. In roughly half the known examples the protein kinase is regulated by the concentration of 3'5'-cyclic AMP formed, for example, in response to the stimulation of catecholamine β receptors, but in many other cases the factors modulating the various types of protein kinase remain to be identified. There are several known cases of a "cascade" arrangement in which the substrate for one protein kinase is in fact a further protein kinase which in turn modulates the activity of the eventual target enzyme. The glycogen breakdown system falls into this category (see below), and a further example of this will be discussed in connection with thick filament regulation. A considerable degree of amplification is inherent in this type of control, so that a tiny stimulus is capable of producing a large and rapid response.

Although myosin represents the major protein within the thick filaments, there are a number of other minor components which probably serve to stabilize the structure, and cross-link the individual thick filaments at the level of the M line. With a molecular weight of 460 000 daltons, myosin is one of the largest proteins in the body; nevertheless, about 250 myosin molecules are required to construct a single thick filament. The protein has a complex internal structure in which a pair of globular head-groups are joined to a long tail with a high α-helix content. It is very likely that the tails are aligned along the axis of the thick filament so that the head groups lie on the surface of the cigar-like aggregate in a repeating helical pattern. The thick filaments are symmetrical about the M line, so that individual myosin molecules have opposite orientations in the two halves of the sarcomere, thereby allowing both sets to pull their respective thin filaments towards the M line during a contraction. The myosin ATPase activity is located in the head groups. In relaxed muscle this enzyme exists in an energized conformation containing tightly bound ADP at its active centre, but during contraction the ADP is released and the energy stored within the myosin molecule becomes available to drive the contractile process. The enzymic mechanism of the myosin ATPase has recently been reviewed by Trentham (1977).

Each myosin molecule comprises two large subunits of 200 000 daltons which make up the tail and part of each head group together with four "light chains" in the range 15 000–30 000 daltons, which are confined to the head groups. Two such light chains (commonly referred to as alkali light chains 1 and 2 after the method of preparation) seem to be involved in actin binding (Winstanley, Trayer and Trayer, 1977), while the other pair (commonly called DTNB light chains) apparently fulfil a regulatory role (Hozumi and Hotta, 1978). The DTNB light chains are able to bind calcium ions, and can be reversibly phosphorylated by a specific myosin light chain kinase (Pires and Perry, 1977) and myosin light chain phosphatase (Morgan, Perry and Ottoway, 1976). Current thinking inclines to the view that calcium binding by myosin light chains has only vestigial significance in mammalian muscles, although in molluscs contractile regulation by calcium ions resides principally in the myosin molecule (Goldberg and Lehman, 1978), and several other invertebrates exhibit a dual thick+thin filament regulatory system (Konno, 1978). However, myosin light-chain kinase is itself sensitive to regulation by calcium ions, and there is increasing evidence that the calcium-dependent phosphorylation of myosin light chains plays a major role in contractile activation in numerous vertebrate smooth muscles (Barron, Barany and Barany, 1979; Lebovitz and Cooke, 1979).

Myosin light-chain kinase consists of two protein subunits: the larger (105 000 daltons) contains the catalytic centre, while the smaller (17 000 daltons) confers sensitivity to calcium ions. This smaller subunit is apparently identical to "modulator protein" (calmodulin) independently isolated from brain and a variety of other mammalian tissues, which is responsible for the calcium sensitivity of phosphorylase kinase, adenyl cyclase, cyclic nucleotide phosphodiesterase and the red cell calcium activated ATPase (Dabrowska et al., 1978; Yagi et al., 1978). Modulator protein is extremely similar to troponin C in amino acid sequence, and the two proteins, although distinct, can partially substitute for one another. This strongly suggests a common evolutionary origin for both proteins from a single ancestral gene (Perry et al., 1979).

Myosin light-chain kinase from turkey gizzard is partially inhibited after phosphorylation by cyclic AMP-dependent protein kinase (Adelstein et al., 1978). This observation immediately suggests a possible mechanism for the relaxation brought about by β-adrenergic agonists in visceral smooth muscle, although it would be premature to suggest that this "cascade" mechanism need be the only pathway involved. Light-chain kinase and phosphatase are in no sense confined to smooth muscle, and it is well established that changes in myosin phosphorylation state occur in response to physiological stimuli in both cardiac and skeletal muscles (Barany et al., 1979). The precise mechanism and functional significance of these changes remain to be identified at present.

Distinct myosin isoenzymes are present in each of the major muscle types (Barany, 1967; Sarkar, Sreter and Gergely, 1971), and even a single fibre type may contain multiple isoenzymes (Hoh et al., 1979) which change during development (Hoh, 1979), and after hormonal stimulation (Flink, Rader and Morkin, 1979). These differences encompass both the heavy and the light chains, and are correlated with contraction speed: fast muscle myosins have inherently greater ATPase activities than those from slow muscles. These differences in enzyme activity result in valuable economies of ATP hydrolysis in slowly contracting muscles which are often required to sustain tension for long periods. The limiting example is provided by molluscan "catch" muscles (Twarog, 1976; Cooley, Johnson and Krause, 1979), which are able to maintain tension in the absence of ATP breakdown for several hours.

The organization of the actin and myosin aggregates differs fundamentally between smooth and striated muscles. In smooth muscle the actin : myosin molar ratio of 15 : 1 is more than double the value observed in striated muscles, and the extreme lability of the myosin aggregates in smooth muscle suggests that the thick filaments are in equilibrium with myosin in a soluble, dissociated form. Suzuki and others (1978) have recently reported that light-chain phosphorylation helps to stabilize smooth muscle myosin in the aggregated state, although it is still far from clear whether the thick filaments have the conventional bipolar cigar shape familiar in striated muscle, or whether they possess a ribbon-like structure in which the head groups are confined to one side (Schoenberg and Needham, 1976). There are no Z lines in smooth muscle, and the thin filaments are instead inserted into numerous "dense bodies" which appear to fulfil an analogous function. Dense bodies contain α-actinin, which is an established Z-line component, and, although the majority are found free in the cytoplasm, a significant number seem to be firmly attached to the cell wall (Somlyo, 1978). Troponin seems to be at best a minor component of the thin filaments in smooth muscle, although tropomyosin has been positively identified, and apparently undergoes a conformational change during contraction. Ebashi and his associates (Hirata et al., 1978) have isolated a protein, "leiotonin", of 90 000 daltons which they claim confers calcium sensitivity to smooth muscle thin filaments, although the majority view continues to favour myosin-linked regulation at present (Murphy, 1978). A third type of filament, the 10-nm or "intermediate" filaments also seem to be associated with the dense bodies in smooth muscle, and closely resemble rather similar filaments seen in a variety of non-muscle cells. Although the function of the intermediate filaments is not understood, it seems unlikely that they constitute an integral part of the contractile apparatus.

EXCITATION–CONTRACTION COUPLING

At first sight there would appear to be profound differences in the mechanism of excitation–contraction coupling between the various types of muscle tissue. The contractile properties of skeletal muscles are scarcely affected by the concentrations of circulating hormones, and remain largely intact when the muscle is bathed in calcium-free media. Depolarization and contraction are tightly coupled, "all-or-none" events, and the force of contraction is controlled digitally by the central nervous system through the dual mechanisms of twitch summation and motor unit recruitment. Cardiac muscle also exhibits all-or-none contractions, but in this tissue the size of the "all" is variable, since the cells are sensitive to a variety of circulating hormones, to stimulation frequency, and to the concentration of ionized calcium in the extracellular fluid. In smooth muscle it is often pointless to speak of all-or-none effects, since it is relatively easy to produce graded changes in membrane potential and developed tension by manipulating the concentrations of hormones, drugs and calcium ions in the fluid bathing the cells (Siegel, Ehehalt and Koepchen, 1978). Indeed, some varieties of smooth muscle lack the obligatory correlation between depolarization and contraction which is normally such a prominent feature of the striated muscle types.

Closer examination, however, reveals a considerable degree of biochemical similarity between the various types of muscle tissue. In each case the resting membrane potential arises from the operation of the sodium/potassium ATPase in conjunction with the differing passive membrane permeabilities for sodium and potassium ions. There is argument as to why the resting membrane potential in smooth muscle should be less (40–60 mV) than in striated muscle (80 mV) but it now seems likely that this arises from opposed fluxes of chloride ions (sodium-linked uptake balanced by an electrogenic efflux) in smooth muscle, which would lead to a partial depolarization. It is significant that a number of widely used vasodilator drugs have proved to be inhibitors of chloride transport in smooth muscle preparations (Kreye, 1978). Sustained oscillations in developed tension and membrane potential have been observed in many types of smooth muscle, and these appear to be linked to metabolic events (Linke and Betz, 1977), although it is not always easy to distinguish cause from effect in these preparations.

The fast sodium channels responsible for the rapid upstroke of the action potential seem to be fundamentally similar in heart and skeletal muscle, even though they may differ in their sensitivity to local anaesthetics and tetrodotoxin. The fast channels have only minor importance in smooth muscle, where the bulk of the current during "spike" discharges is carried by calcium ions (Kuriyama, Ito and Suzuki, 1977). There seems to be a surprising degree of similarity between these slow, electrogenic calcium channels in the various types of muscle. They are readily blocked by lanthanum ions, and by verapamil in skeletal muscle (Sanchez and Stefani, 1978) as well as in cardiac muscle and smooth muscle (Fleckenstein, 1977). Calcium entry is enhanced during activity in all types of muscle, although in skeletal muscle the abbreviated action potential permits only insignificant quantities of calcium to enter during a single twitch. In cardiac muscle integration of the slow inward current during the plateau phase of the action potential suggests that up to 10% of the calcium needed for contractile activation may cross the plasmalemma during each beat (Langer, 1976). In smooth muscle, however, it is theoretically possible for the whole of the calcium to enter from the outside.

There are at present two possible mechanisms whereby calcium might be released from the sarcoplasmic reticulum in order to activate muscular contractions (Endo, 1977; Fabiato and Fabiato, 1977). It is thought that in skeletal muscle, membrane depolarization is transmitted via the T-tubules to the adjacent sarcoplasmic reticulum, thereby initiating the release process, while for cardiac muscle it is believed that "trigger calcium" entering during the plateau phase of the action potential initiates an autocatalytic release of additional calcium from the sarcoplasmic reticulum. This "calcium-induced calcium release" can be observed *in vitro* using isolated vesicles derived from cardiac sarcoplasmic reticulum (see, for example, Kirchberger and Wong, 1978), but in skeletal muscle the corresponding process is inhibited by physiological magnesium concentrations (Katz et al., 1977). It is not clear why the sarcoplasmic reticulum in normal muscle should suddenly switch back to calcium accumulation when a contraction terminates. Reiser and others (1979) have recently presented some remarkable results on disaggregated adult cardiac muscle cells, which seem to be functionally equivalent to the "skinned" muscle cells previously used by Fabiato and Fabiato (1977), in that the plasmalemma is electrically inexcitable, and appears to be freely permeable to small ions. At an external calcium concentration of 1 μmol litre^{-1} the cells exhibit rhythmic contractions which begin at one end and propagate along the cell, suggesting that calcium released at one point is indeed able to trigger release of calcium in neighbouring sarcomeres. Studies of the force–frequency relationship in cardiac muscle strongly suggest that trigger calcium entering during the action potential is temporarily re-accumulated within the sarcoplasmic reticulum, and participates in contractile activation for several beats before it is finally re-exported from the tissue (Allen, Jewell and Wood, 1976).

It has been known for many years that the force of contraction varies with the initial fibre length in all types of muscle, and with the advent of the cross-bridge theory it became fashionable to attribute these variations to changes in the effective overlap between the thick and thin filaments. More recently, Jewell (1977) has argued the importance of length-dependent contractile activation in cardiac muscle in order to explain the decline in tension at short sarcomere lengths, and there is evidence from experiments with skinned muscle fibres that a similar situation also obtains in skeletal muscle.

Langer (1976) has challenged the whole basis of the preceding discussion of sarcoplasmic reticulum function, and claimed that large amounts of calcium enter each cardiac cell by an electrically silent exchange with sodium ions during every action potential, thereby obviating any need for calcium-induced calcium release. This view deserves to be taken seriously, since Langer and his associates have been responsible for a large proportion of the isotopic flux measurements made to date; nevertheless, in the majority of cases, an alternative explanation can be devised for their results which is consistent with the conventional wisdom as outlined above.

Calcium export from muscle tissues almost certainly involves a reciprocal exchange with sodium ions, but unfortunately there is little agreement on the precise stoichiometry of this process. Many authors originally assumed an electroneutral exchange of 2 Na$^+$ for 1 Ca^{2+}, although this does not provide sufficient driving force to pump calcium out of the cells under physiological conditions without an additional energy input. As a result, Blaustein (1976) suggested a ratio of 3 : 1 and Mullins (1979) has proposed that the ratio may be as great as 4 Na^+ for 1 Ca^{2+}. Recent measurements by Pitts (1979) yielded a value of 3 : 1 in cardiac sarcolemmal vesicles, while the observation that sodium-dependent calcium efflux from cardiac muscle was scarcely affected by a four-fold reduction in extracellular sodium (Wendt and Langer, 1977) implies that there must be a substantial outward driving force for calcium export, which is consistent with an increased sodium : calcium ratio in the intact tissue. Physiological extracellular sodium concentrations apparently inhibit the electrogenic calcium influx mechanism, since Wendt and Langer also reported that calcium influx was stimulated in low-sodium media. This would explain the inotropic effects which follow a reduction in the extracellular sodium concentration. The inotropic response to cardiac glycosides, on the other hand, is apparently associated with an increase in the intracellular sodium concentration. It is widely (though not universally) believed that these drugs act by inhibiting the plasmalemma Na^+/K^+ATPase, thereby increasing the intracellular sodium concentration and retarding sodium-dependent calcium efflux from the heart.

In addition to the sodium-linked efflux mechanism (Ma and Bose, 1977), a number of authors have reported the presence of a Ca^{2+} ATPase in the plasma membrane of smooth muscle cells and heart (Åkerman and Wikström, 1978). If confirmed, this would be analogous to the calcium export mechanism in red blood cells, although the evidence for a sarcolemmal location for this enzyme in smooth muscle cannot be regarded as definitive at present. There remains the intruiging possibility that one or more of the sarcolemmal calcium transport channels might communicate directly with the sarcoplasmic reticulum as opposed to the myofibrillar compartment. In striated muscle the specialized junctions between the sarcoplasmic reticulum and the T-tubules (Nayler, 1975; Caswell et al., 1979) would be obvious sites for this type of transport system, while in smooth muscle there are homologous structures formed between the sarcoplasmic reticulum and the surface microvesicles (caveolae) which are a prominent feature of this tissue (Somlyo and Somlyo, 1976). The energetics of this type of carrier would be very different from a channel communicating with the myofibrillar space, since the free calcium concentration within the sarcoplasmic reticulum is probably comparable to that in the extracellular space. The presence of calcium-binding proteins of low affinity and high capacity within the lumen of the sarcoplasmic reticulum enables the total calcium-carrying capacity to exceed the free concentration by a considerable factor (MacLennan and Wong, 1971; Caudwell, Antoniw and Cohen, 1978).

EFFECTS OF HORMONES AND NEUROTRANSMITTERS

It is no longer seriously disputed that catecholamines accelerate glycogen breakdown in striated muscle through a system of protein kinases which is regulated by cyclic AMP, and which acts in concert with a calcium-based regulatory mechanism and additional metabolic feedbacks from the glycolytic pathway (Cohen, 1979). As a result it is tempting to look to the cyclic nucleotide-dependent protein kinases in the search for other common mechanisms of hormone action on muscle tissue, even though the effects of acetylcholine and catecholamines on contractile performance in the heart, for instance, are diametrically opposed to their actions on smooth muscle.

Diamond (1978) has argued cogently against the over-enthusiastic application of such theories to smooth muscle, while Drummond and Severson (1979) have critically reviewed the available data on the heart. Nevertheless there does seem to be good evidence that at least some of the effects of hormones and neurotransmitters on contractile performance in cardiac and smooth muscles are mediated via changes in cyclic nucleotide concentrations, even if there are other effects which cannot be explained in this way.

Protein kinase modulation of cardiac troponin I and smooth muscle myosin light-chain kinase have already been discussed in the previous section on the contractile apparatus. An additional mechanism which seems to be operative in cardiac muscle involves the phosphorylation of a minor sarcoplasmic reticulum component, "phospholamban", by cyclic AMP-dependent protein kinase. This results in a greatly increased rate of ATP-dependent Ca^{2+} accumulation which can readily be studied *in vitro* using vesicular preparations of sarcoplasmic reticulum and added, exogenous protein kinase (Hicks, Shigekawa and Katz, 1979; Tada et al., 1979). It is likely that, *in vivo*, the phosphorylation is catalysed by an endogenous protein kinase, which is present in increased amounts in hyperthyroid animals (Limas, 1978). The increased velocity of calcium uptake in response to an increased intracellular concentration of cyclic AMP is thought to contribute to the increased

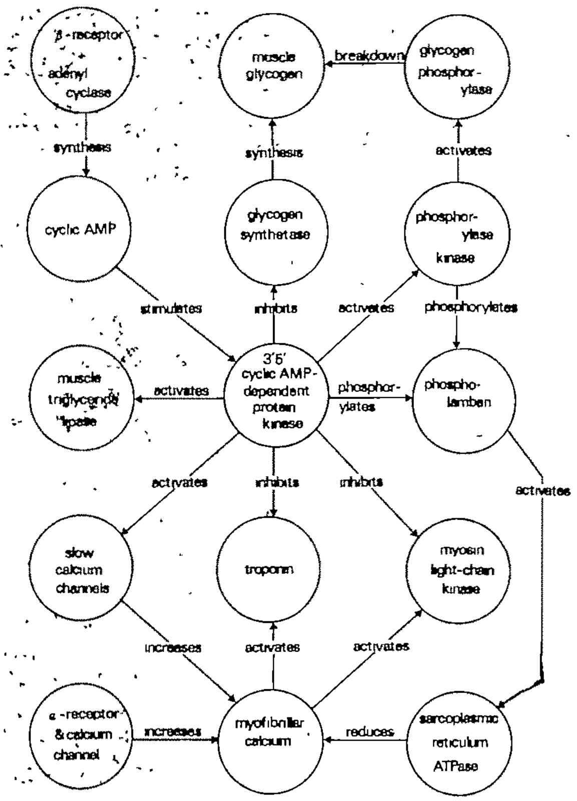


FIG. 2. Protein kinase-mediated hormonal effects in muscle. In non-stimulated muscle, cyclic AMP-dependent protein kinase exists as an inactive complex with its two regulatory subunits. Cyclic AMP is able to bring about the dissociation of this complex by binding to the regulatory subunits, and thereby releases the active catalytic subunits after β-adrenergic stimulation. The calcium channel, which is probably activated by α-adrenergic stimulation, is not necessarily identical with the voltage-dependent calcium channel responsible for the slow inward current, which appears to be modulated via the β-adrenoceptor system.

rate of relaxation observed in cardiac muscle under the influence of hormones such as histamine, glucagon and the catecholamines (fig. 2).

The inotropic actions of catecholamines and related hormones on cardiac muscle probably involve a cyclic AMP-stimulated phosphorylation of a protein associated with the slow, electrogenic calcium entry channels in the plasmalemma, leading to an enhancement of the slow inward current, and an increase in the myocardial calcium content (Reuter and Scholz, 1977; Josephson and Sperelakis, 1978; Jones et al., 1979; Keely and Eiring, 1979). In addition to the β-adrenergic responses mediated via cyclic AMP, it has recently become apparent that cardiac muscle possesses an appreciable number of α-adrenergic receptors, and that the α : β ratio is decreased in hyperthyroid animals (Williams et al., 1977; Sharma and Banerjee, 1978). In view of the fact that α-adrenergic stimulation is reported to decrease the cyclic AMP concentrations in rat heart (Watanabe et al., 1977), it is to be anticipated that the catecholamine action mechanism will depend on the agonist and dose employed, the duration of the experiment, and the previous hormonal history of the animals.

Cholinergic agonists antagonize the actions of catecholamines in cardiac muscle, and it has been suggested that this muscarinic effect is mediated at least partly via the action of cyclic GMP (Watanabe and Besch, 1975; Keely, Lincoln and Corbin, 1978; Kohlhardt and Haap, 1978). Cyclic GMP has also been implicated in the slow decline in cardiac contractility which is seen during prolonged exposure to catecholamines (Singh, Flitney and Lamb, 1978). Despite the purification of a cyclic GMP-dependent protein kinase (Flockerzi, Speichermann and Hofmann, 1978) and a stimulatory modulator protein (Shoji et al., 1978) from heart muscle, the mechanism of action of cyclic GMP remains almost completely unknown at the present time.

The initial rapid relaxation produced by isoproterenol in smooth muscle is not apparently connected with cyclic nucleotides (Schiff and Overweg, 1978), but there are clear indications that the delayed relaxation brought about by β-adrenergic agonists is mediated by cyclic AMP (Honeyman, Merriam and Fay, 1978). Possible mechanisms include the phosphorylation (and inhibition) of myosin light-chain kinase (Adelstein et al., 1978) and the stimulation of calcium removal from the myofilaments through an effect on a calcium transport system (Bhalla et al., 1978; Nishikori and Maeno, 1979). Evidence is accumulating against any obligatory role for cyclic GMP as a mediator of muscarinic cholinergic contractions in smooth muscle (see, for example, Lohmann, Miech and Butcher, 1977; Leiber, Vesin and Harbon, 1978) and, indeed, cyclic GMP concentrations are substantially increased by sodium nitroprusside and a number of other agents which normally lead to the relaxation of smooth muscle preparations (Schulz, Schulz and Schulz, 1977). Current thinking is plainly moving in favour of some direct effect on plasmalemma ion transport as an early event in the muscarinic response, which would be analogous to the well-established sodium ionophore linkage to the nicotinic receptors at the skeletal neuromuscular junction (Shorr, Dolly and Barnard, 1978; Changeux et al., 1979).

INTERMEDIARY METABOLISM

The detailed mechanism whereby the external work-load controls the rate of muscle substrate metabolism has gradually become clearer in recent years. A long-standing problem has been the substantial ADP and AMP content in resting muscles, which is superficially incompatible with the known properties of muscle regulatory enzymes, such as phosphofructokinase (Mansour, 1972) and glycogen phosphorylase (Schliselfeld, Davis and Krebs, 1970). Although it is frequently claimed that a large amount of ADP is bound to actin and myosin in muscle, the data of Perry (1952) suggest that only 30% of the ADP is bound in this way. It now seems likely that a substantial part of the remaining discrepancy stems from the active sequestration of ADP and AMP within the mitochondria, and the associated active export of mitochondrial ATP into the myofibrillar space (Illingworth et al., 1975; Nishiki, Erecinska and Wilson, 1978; Veech et al., 1979). As a result, highly significant changes in the small myofibrillar pools of free ADP and AMP are masked by much larger invariant ADP and AMP pools within the mitochondria, although it is, apparently, the extramitochondrial pools which control both the respiratory and the glycolytic rates. Many other metabolites are also asymmetrically distributed across the mitochondrial inner membrane (see LaNoue and Schoolwerth (1979) for a recent review), and it is plain that this situation has enormous regulatory implications. In particular, it is the active transport of aspartate out of the mitochondria which ultimately permits the re-oxidation of glycolytic NADH within the extra-mitochondrial space by the intramitochondrial respiratory chain (Meijer and VanDam, 1974), and it is the existence of this "malate–aspartate shuttle" which prevents the formation of lactate by oxidative muscles under normal physiological conditions.

Diffusion problems posed by the very small extramitochondrial free-ADP concentration have prompted the suggestion that creatine and creatine phosphate are the mobile species which transport high-energy phosphate groups through the myofibrils (Altschuld and Brierley, 1977; Saks et al., 1978). This theory, which is by no means universally accepted (Newsholme et al., 1978), envisages creatine phosphate synthesis by the perimitochondrial creatine kinase isoenzyme, balanced by the subsequent regeneration of ATP by the distinct myofibrillar creatine kinase protein. The alternative viewpoint continues to regard creatine phosphate as a buffer store which acts to prevent excessive changes in ATP and ADP concentrations during a contraction. In any event, it is no longer so difficult to understand why huge alterations in glycolytic flux and oxygen utilization can occur after changes in muscle work load without corresponding variations in the whole tissue adenine nucleotide concentrations, although alterations in creatine phosphate content can be readily observed. Moreover, it is the small and highly variable extramitochondrial AMP pool which is the immediate precursor for adenosine production in muscle tissue, and this provides an obvious explanation for the increased adenosine output observed during exercise and during hypoxic stress. In addition to reducing cardiac cyclic AMP concentrations (Dobson, 1979), adenosine has a major role in the local regulation of coronary blood flow under physiological conditions (Belloni, 1979; Watkinson et al., 1979), and there is strong evidence for a similar function in skeletal muscle and other tissues. An excellent review of adenosine biochemistry has recently been published by Arch and Newsholme (1978).

Myofibrillar AMP also participates in the reactions of the purine nucleotide cycle (Lowenstein and Goodman, 1978) which is responsible for ammonia production by working skeletal muscles. This reaction sequence is largely confined to skeletal muscle, where it is closely integrated with the glycolytic pathway, and apparently serves to generate essential citric acid cycle intermediates *de novo* from aspartic acid when the muscle work-load increases. It should be noted that muscle cells contain little or no glutamate dehydrogenase or pyruvate carboxylase, the two enzymes which are largely responsible for replenishing citric acid cycle intermediates in liver tissue. The branched-chain amino acids, isoleucine and valine, can also be converted into citric acid cycle intermediates in muscle, and a number of other amino acids must suffer a similar fate, although their degradation rates are poorly characterized at present (Garber, Karl and Kipnis, 1976a, b). It is apparent that there must also exist an exit route from the citric acid cycle if the concentrations of cycle intermediates are to be stabilized in the physiological range. Lee and Davis (1979) suggest that emptying requires the participation of NAD- and NADP-linked malic enzymes, while Newsholme and Williams (1978) and Snell and Duff (1977) both suggest an important role for PEP carboxykinase, an enzyme more usually associated with hepatic gluconeogenesis. Both these exit routes lead to the formation of pyruvate, most of which must be transaminated with glutamate to yield oxoglutarate and alanine. The alanine is finally exported from the tissue, but the oxoglutarate undergoes an additional transamination, which permits a further amino acid molecule to embark on the degradative pathway while simultaneously maintaining the tissue glutamate pool. An alternative exit route also involves the transamination of oxoglutarate with an incoming amino acid to yield glutamate, but in this case the glutamate is further metabolized to glutamine and subsequently exported from the cell. These reactions are summarized in figure 3. Alanine and glutamine together account for the bulk of the amino acids released from skeletal muscle during starvation, when they assume considerable importance since alanine is the preferred substrate for hepatic gluconeogenesis, while glutamine is required for urinary pH regulation and renal glucose production.

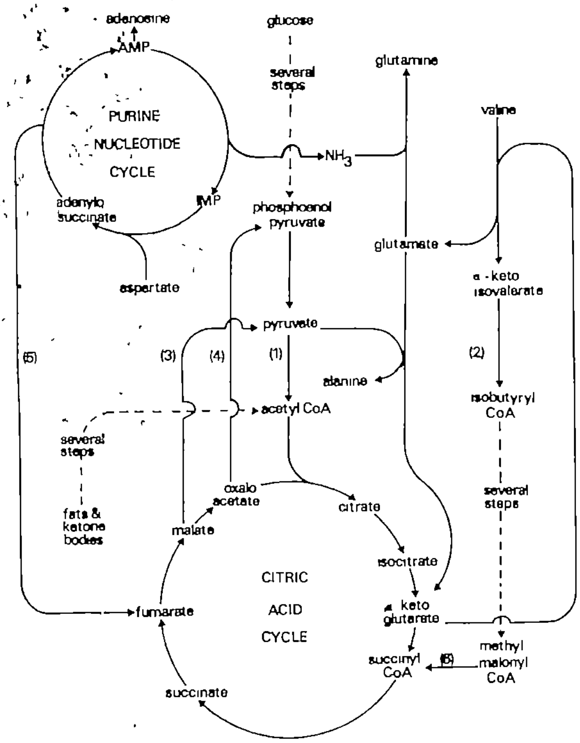


FIG. 3. Metabolic interrelationships involved in muscular amino acid degradation. In the interests of clarity the distinction bewteen mitochondrial and extramitochondrial metabolism has been ignored in this diagram. With the exception of the glycolytic pathway and the purine nucleotide cycle, the majority of these reactions occur within the mitochondria. Reaction (1) is pyruvate dehydrogenase, while (2) is the analogous reaction undergone by branched-chain amino acid carbon skeletons, which is referred to in the text. Reactions (3) and (4) represent the "malic" enzymes and PEP-carboxykinase respectively, which constitute the major exit routes from the citric acid cycle for the material injected by reactions (5)—adenylosuccinate lyase, and (6)—vitamin B_{12}-dependent methylmalonyl CoA mutase. It should be noted that a large number of cofactors and coenzymes have been omitted from this diagram in the interests of clarity, and that the details of most of the individual reactions can be found in a number of modern biochemistry textbooks.

A number of authors, including Chang and Goldberg (1978a), have challenged the interpretation presented above and suggested, on the basis of isotopic flux measurements and inhibitor studies, that the carbon atoms which make up the alanine released from skeletal muscle are derived from glucose, rather than amino acids. They propose a "glucose–alanine cycle" which would be closely analogous to the well-known Cori cycle (Krebs, Woods and Alberti, 1975) in which lactate formed during muscular glycolysis is reconverted to blood glucose by the liver. The glucose–alanine cycle *per se* cannot possibly account for the net conversion of the amino acid content of skeletal muscle proteins into blood glucose during starvation, and Chang and Goldberg (1978b) suggest instead that it is the glutamine exported by skeletal muscle which supports *de novo* glucose synthesis under these conditions. This suggestion is plainly inconsistent with the data of Karl, Garber and Kipnis (1976a), who showed that a number of circumstances such as fasting, cortisone treatment and diabetes, which are normally associated with an enhanced rate of gluconeogenesis, nevertheless inhibited glutamine release from skeletal muscle, and increased the output of alanine.

The breakdown of muscle proteins to yield glucose precursors during starvation is subject to precise hormonal regulation. Large doses of cortisol undoubtedly lead to muscle wasting (Tomas, Munro and Young, 1979), although small doses are without effect, while in the presence of insulin corticosteroids may actually have an anabolic action on fetal heart cells in organ culture (Griffin and Wildenthal, 1978). Insulin is required for effective protein synthesis in muscle, and Li, Higgins and Jefferson (1979) have suggested that insulin withdrawal increases amino acid release during starvation by preventing the resynthesis of muscle proteins, while Shoji and Pennington (1977) have suggested that cortisol administration produces a rather similar effect. Garber, Karl and Kipnis (1976c) have shown that catecholamines inhibit protein degradation in rat skeletal muscle, and that this effect is mediated via the β receptors and cyclic AMP. In contrast to this, cholinergic agonists apparently accelerate muscle protein breakdown and release (Garber, Entman and Birnbaumer, 1978) through a mechanism involving nicotinic receptors and (surprisingly) cyclic GMP. Under steady-state conditions, red muscle proteins turn over nearly twice as fast as white muscle proteins (Millward, 1978), although there is considerable uncertainty about the factors which regulate total muscle mass in well-fed individuals. Overload, which in practice implies a high frequency of intense isometric contractions, is a powerful stimulus to muscle growth, and there is now good evidence for a role for ornithine decarboxylase in this process (Feldman and Russell, 1972; Matsushita, Sogani and Roben, 1972). This enzyme represents the first step on the pathway of polyamine biosynthesis, the compounds of which will eventually function as essential cofactors for the protein synthetic machinery in hypertrophying muscle. Denervated muscles regress towards the enzyme profile found in embryonic muscle (Ilyin, Razumovska and Usatenko, 1975), while re-innervation results in a return to the glycolytic and oxidative enzyme profiles characteristic of the motor neurone type (Pette and Dolken, 1974).

As previously mentioned in connection with fibre classification, the energy sources for muscle contraction vary with fibre type. The type 2B fibres have little option but to make use of stored glycogen (Griffiths and Rahim, 1978), but in other muscle cells in which the enzyme complement permits a choice of substrate, the balance can be tilted away from fats and towards carbohydrates by circulating insulin, partly as a result of improved glucose transport into the tissue. It is important to realize that under normal circumstances the various possible substrates for oxidation by heart and red skeletal muscles (free fatty acids, ketone bodies, triglycerides, branched-chain amino acids, pyruvate, lactate and glucose) are in a state of mutual competition, so that the precise mixture oxidized by the tissue will depend on the relative availability of each compound, which in turn will be a function of the dietary and hormonal status of the organism (Neely and Morgan, 1974; Maizels et al., 1977; Rennie and Holloszy, 1977). Leucine oxidation (Odessey and Goldberg, 1979) apparently has some special regulatory significance for skeletal muscle, since it inhibits carbohydrate oxidation in muscle from fasted rats, but not in tissue taken from well-fed animals (Chang and Goldberg, 1978c). There is now some evidence that the enzyme responsible for the oxidative decarboxylation of the oxo-acids derived from valine, leucine and isoleucine is subject to regulation by a phosphorylation–dephosphorylation cycle (Parker and Randle, 1978), in a manner analogous to pyruvate dehydrogenase, which is discussed below.

The pro-lipid bias of most oxidative muscles (Zierler, 1976) assumes considerable importance during fasting when it is essential to conserve carbohydrate reserves. Without wishing to belittle the importance of glycogen phosphorylase (Cohen, 1978, 1979) and phosphofructokinase (Newsholme and Start, 1973; Ramaiah, 1976), recent years have seen a growing interest in metabolic regulation at the level of pyruvate dehydrogenase, which is now regarded as the central point of competition between fat and carbohydrate substrates (Denton et al., 1975). This mitochondrial enzyme is subject to regulation by a specific protein kinase and phosphoprotein phosphatase, which have proved to be completely insensitive to cyclic nucleotides, and to respond instead to metabolic stimuli, such as the ratios of NADH : NAD, ATP : ADP and acetyl CoA : CoASH (Hansford, 1977). A plausible mechanism for this regulation has been described by Cate and Roche (1978, 1979), who suggest that enzyme molecules bearing a reduced or acetylated dihydrolipoyl cofactor are particularly susceptible to inactivation by the protein kinase. Reactivation by the phosphoprotein phosphatase is markedly stimulated by small concentrations of calcium ions, but, conversely, the phosphorylation of additional regulatory sites on the pyruvate dehydrogenase molecule greatly retards the rate of the phosphatase reaction (Sugden et al., 1978).

It should be apparent from this discussion that the metabolic capacities of muscle tissue are more extensive and varied than was previously supposed. Indeed, recent work by McLane and Holloszy (1979) has shown that the glycolytic fibre types 2A and 2B possess appreciable activities of the gluconeogenic enzyme fructose-1,6-bisphosphatase and are able to synthesize glycogen from circulating lactate. This pathway was previously considered to reside almost exclusively in the liver. Despite the fact that many of these novel pathways proceed relatively slowly per kilogram of muscle, the total weight of contractile tissue in the body is so large that intermediary metabolism in muscle must make a sustantial contribution to the overall energy and susbtrate balance of the intact organism.

REFERENCES

Adelstein, R. S., Conti, M. A., Hathaway, D. R., and Klee, C. B. (1978). Phosphorylation of smooth muscle myosin light-chain kinase by the catalytic subunit of cAMP-dependent protein kinase. *J. Biol. Chem.*, **253**, 8347.

Åkerman, K. E., and Wikström, M. K. F. (1978). (Ca^{++} + Mg^{++})-stimulated ATPase activity of rabbit myometrium plasma membrane is blocked by oxytocin. *FEBS Lett.*, **97**, 283.

Allen, D. G., Jewell, B. R., and Wood, R. H. (1976). Studies on the contractility of mammalian myocardium at low rates of stimulation. *J. Physiol. (Lond.)*, **254**, 1.

Altschuld, R. A., and Brierley, G. P. (1977). Interaction between creatine kinase of heart mitochondria and oxidative phosphorylation. *J. Molec. Cell. Cardiol.*, **9**, 875.

Amphlett, G. W., Perry, S. V., Syska, H., Brown, M. D., and Vrbova, G. (1975). Cross innervation and the regulatory protein system of rabbit soleus. *Nature (Lond.)*, **257**, 602.

Arch, J. R. S., and Newsholme, E. A. (1978). The control of the metabolism and the hormonal role of adenosine. *Essays Biochem.*, **14**, 82.

Bailin, G. (1979). Phosphorylation of a bovine cardiac actin complex. *Am. J. Physiol.*, **236**, C41.

Barany, K., Barany, M., Gillis, J. M., and Kushmeric, M. J. (1979). Phosphorylation–dephosphorylation of the 18 000-dalton light chain of myosin during the contraction–relaxation cycle of frog muscle. *J. Biol. Chem.*, **254**, 3617.

Barany, M. (1967). ATPase activity of myosin correlated with the speed of muscle shortening. *J. Gen. Physiol.*, **50** (Suppl.), 197.

Barron, J. T., Barany, M., and Barany, K. (1979). Phosphorylation of the 20 000-dalton light chain of myosin of intact arterial smooth muscle in rest and in contraction. *J. Biol. Chem.*, **254**, 4954.

Belloni, F. L. (1979). The local control of coronary blood flow. *Cardiovasc. Res.*, **13**, 63.

Bhalla, R. C., Webb, R. C., Singh, D., and Brock, T. (1978). Role of cyclic AMP in rat aortic microsomal phosphorylation and calcium uptake. *Am. J. Physiol.*, **234**, H508.

Blaustein, M. P. (1976). Sodium–calcium exchange and the regulation of cell calcium in muscle fibres. *Physiologist*, **19**, 525.

Carafoli, E., and Crompton, M. (1978). The regulation of intracellular calcium. *Curr. Top. Membranes Transp.*, **10**, 151.

Caswell, A. H., Lau, Y. H., Garcia, M., and Brunschwig, J.-P. (1979). Recognition and junction formation by isolated transverse tubules and terminal cisternae of skeletal muscle. *J. Biol. Chem.*, **254**, 202.

Cate, R. L., and Roche, T. E. (1978). A unifying mechanism for stimulation of mammalian pyruvate dehydrogenase kinase by reduced nicotinamide adenine dinucleotide, dihydrolipoamide, acetyl coenzyme A, or pyruvate. *J. Biol. Chem.*, **253**, 496.

—— —— (1979). Function and regulation of the mammalian pyruvate dehydrogenase complex. *J. Biol. Chem.*, **254**, 1659.

Caudwell, B., Antoniw, J. F., and Cohen, P. (1978). Calsequestrin, myosin, and the components of the protein–glycogen complex in rabbit skeletal muscle. *Eur. J. Biochem.*, **86**, 511.

Chang, T. W., and Goldberg, A. L. (1978a). The origin of the alanine produced by skeletal muscle. *J. Biol. Chem.*, **253**, 3677.

—— —— (1978b). The metabolic fates of the amino acids and the formation of glutamine in skeletal muscle. *J. Biol. Chem.*, **253**, 3685.

—— —— (1978c). Leucine inhibits oxidation of glucose and pyruvate in skeletal muscle during fasting. *J. Biol. Chem.*, **253**, 3696.

Changeux, J.-P., Heidmann, T., Popot, J.-L., and Sobel, A. (1979). Reconstitution of a functional acetylcholine regulator under defined conditions. *FEBS Lett.*, **105**, 181.

Clarke, M., and Spudich, J. A. (1977). Non-muscle contractile proteins: the role of actin and myosin in cell motility and shape determination. *Annu. Rev. Biochem.*, **46**, 797.

Cohen, P. (1978). The role of cyclic AMP-dependent protein kinase in the regulation of glycogen metabolism in mammalian skeletal muscle. *Curr. Top. Cell. Regulat.*, **14**, 117.

—— (1979). The hormonal control of glycogen metabolism in mammalian muscle by multivalent phosphorylation. *Biochem. Soc. Trans.*, **7**, 459.

Cooley, L. B., Johnson, W. H., and Krause, S. (1979). Phosphorylation of paramyosin and its possible role in the catch mechanism. *J. Biol. Chem.*, **254**, 2195.

Crompton, M., Moser, R., Ludi, H., and Carafoli, E. (1978). The interrelations between the transport of sodium and calcium in mitochondria of various tissues. *Eur. J. Biochem.*, **82**, 25.

Cummins, P., and Perry, S. V. (1974). Chemical and immunochemical characterisation of tropomyosins from striated and smooth muscles. *Biochem. J.*, **141**, 43.

Dabrowska, R., Sherry, J. M. F., Aromatorio, D. K., and Hartshorne, D. J. (1978). Modulator protein as a component of myosin light-chain kinase from chicken gizzard. *Biochemistry*, **17**, 253.

DeMeis, L., and Vianna, A. L. (1979). Energy interconversion by the Ca^{++}-dependent ATPase of the sarcoplasmic reticulum. *Annu. Rev. Biochem.*, **48**, 275.

Denton, R. M., Randle, P. J., Bridges, B. J., Cooper, R. H., Kerbey, A. L., Pask, H. T., Severson, D. L., Stansbie, D., and Whitehouse, S. (1975). Regulation of mammalian pyruvate dehydrogenase. *Molec. Cell. Biochem.*, **9**, 27.

Dhoot, G. K., and Perry, S. V. (1979). Distribution of polymorphic forms of troponin components and tropomyosin in skeletal muscles. *Nature (Lond.)*, **278**, 714.

Diamond, J. (1978). Role of cyclic nucleotides in control of smooth muscle contraction. *Adv. Cyclic Nucleotide Res.*, **9**, 327.

Dobson, J. G. (1979). Reduction by adenosine of the isoproterenol-induced increase in cyclic adenosine 3′5′ monophosphate formation and glycogen phosphorylase activity in rat heart muscle. *Circ. Res.*, **43**, 785.

Drummond, G. I., and Severson, D. L. (1979). Cyclic nucleotides and cardiac function. *Circ. Res.*, **44**, 145.

Dubowitz, V., and Brooke, M. H. (1973). *Muscle Biopsy: A Modern Approach*, p. 44. London: W. B. Saunders.

Ebashi, S. (1974). Regulation of muscle contraction with special reference to the Ca–troponin–tropomyosin system. *Essays Biochem.*, **10,** 1.

Endo, M. (1977). Calcium release from the sarcoplasmic reticulum. *Physiol. Rev.*, **57,** 71.

Fabiato, A., and Fabiato, F. (1977). Calcium release from the sarcoplasmic reticulum. *Circ. Res.*, **40,** 119.

Feldman, M. J., and Russell, D. H. (1972). Polyamine biosynthesis in the left ventricle of the rat heart after aortic constriction. *Am. J. Physiol.*, **222,** 1199.

Fleckenstein, A. (1977). Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. *Annu. Rev. Pharmacol. Toxicol.*, **17,** 149.

Flink, I. L., Rader, J. H., and Morkin, E. (1979). Thyroid hormone stimulates synthesis of a cardiac myosin isozyme. *J. Biol. Chem.*, **254,** 3105.

Flockerzi, V., Speichermann, N., and Hofmann, F. (1978). A guanosine 3′5′ monophosphate-dependent protein kinase from bovine heart muscle. *J. Biol. Chem.*, **253,** 3395.

Garber, A. J., Entman, M. L., and Birnbaumer, L. (1978). Cholinergic stimulation of skeletal muscle alanine and glutamine formation and release. *J. Biol. Chem.*, **253,** 7924.

—— Karl, I. E., and Kipnis, D. M. (1976a). Alanine and glutamine synthesis and release from skeletal muscle: I—glycolysis and amino acid release. *J. Biol. Chem.*, **251,** 826.

—— —— —— (1976b). Alanine and glutamine synthesis and release from skeletal muscle: II—precursor role of amino acids. *J. Biol. Chem.*, **251,** 836.

—— —— —— (1976c). Alanine and glutamine synthesis and release from skeletal muscle: IV—β adrenergic inhibition of amino acid release. *J. Biol. Chem.*, **251,** 851.

Goldberg, A., and Lehman, W. (1978). Troponin-like proteins from the muscles of the scallop, *Aequipecten irridians*. *Biochem. J.*, **171,** 413.

Griffin, E. E., and Wildenthal, K. (1978). Regulation of cardiac protein balance by hydrocortisone: interaction with insulin. *Am. J. Physiol.*, **234,** E306.

Griffiths, J. R., and Rahim, Z. H. A. (1978). Glycogen as a fuel for skeletal muscle. *Biochem. Soc. Trans.*, **6,** 503.

Hansford, R. G. (1977). Studies on inactivation of pyruvate dehydrogenase by palmitoyl carnitine oxidation in isolated rat heart mitochondria. *J. Biol. Chem.*, **252,** 1552.

Head, J. F., Weeks, R. A., and Perry, S. V. (1977). Affinity chromatographic isolation and some properties of troponin C from different muscle types. *Biochem. J.*, **161,** 465.

Heilmann, C., and Pette, D. (1979). Molecular transformations in sarcoplasmic reticulum of fast-twitch muscle by electrostimulation. *Eur. J. Biochem.*, **93,** 437.

Hicks, M. J., Shigekawa, M., and Katz, A. M. (1979). Mechanism by which cyclic adenosine 3′5′ monophosphate-dependent protein kinase stimulates calcium transport in cardiac sarcoplasmic reticulum. *Circ. Res.*, **44,** 384.

Hirata, M., Mikawa, T., Nonmura, Y., and Ebashi, S. (1978). Ca^{++} regulation in vascular smooth muscle. *J. Biochem. (Tokyo)*, **82,** 1793.

Hoh, J. F. Y. (1979). Developmental changes in chicken skeletal muscle isozymes. *FEBS Lett.*, **98,** 267.

Hoh, J. F. Y., Yeoh, G. P. S., Thomas, M. A. W., and Higginbottom, L. (1979). Structural differences in the heavy chains of rat ventricular myosin isoenzymes. *FEBS Lett.*, **97,** 330.

Holloszy, J. O., and Booth, F. W. (1976). Biochemical adaptations to endurance training in muscle. *Annu. Rev. Physiol.*, **38,** 273.

Honeyman, T., Merriam, P., and Fay, F. S. (1978). The effects of isoproterenol on adenosine cyclic 3′5′-monophosphate and contractility in isolated smooth muscle cells. *Molec. Pharmacol.*, **14,** 86.

Hooker, A. M., and Baldwin, K. M. (1979). Substrate oxidation specificity in different types of mammalian muscle. *Am. J. Physiol.*, **236,** C66.

Hozumi, T., and Hotta, K. (1978). Effects of myosin DTNB light chain on the actin–myosin interaction in the presence of ATP. *J. Biochem. (Tokyo)*, **83,** 671.

Huxley, H. E. (1972). Molecular basis of contraction in cross-striated muscles; in *The Structure and Function of Muscle*, vol. 1, 2nd edn (ed. G. H. Bourne), p. 301. London: Academic Press.

Illingworth, J. A., Ford, W. C. L., Kobayashi, K., and Williamson, J. R. (1975). Regulation of myocardial energy metabolism; in *Recent Advances in Studies on Cardiac Structure and Metabolism*, vol. 8 (eds P. E. Roy and P. Harris), p. 271. Baltimore: University Park Press.

Ilyin, V. S., Razumovska, N. I., and Usatenko, M. S. (1975). Influence of nerve impulse on enzyme synthesis in skeletal muscle. *Adv. Enzyme Regul.*, **13,** 219.

Jewell, B. R. (1977). A re-examination of the influence of muscle length on myocardial performance. *Circ. Res.*, **40,** 221.

Jones, L. R., Besch, H. R., Fleming, J. W., McConnaughey, M. M., and Watanabe, A. M. (1979). Separation of vesicles of cardiac sarcolemma from vesicles of cardiac sarcoplasmic reticulum. *J. Biol. Chem.*, **254,** 530.

Josephson, I., and Sperelakis, N. (1978). 5′-Guanylimidodiphosphate stimulation of the slow Ca^{++} current in myocardial cells. *J. Molec. Cell. Cardiol.*, **10,** 1157.

Kaplan, N. O., and Goodfriend, T. L. (1964). Role of the two types of lactate dehydrogenase. *Adv. Enzyme Regul.*, **2,** 203.

Karl, I. E., Garber, A. J., and Kipnis, D. M. (1976). Alanine and glutamine synthesis and release from skeletal muscle: III—dietary and hormonal regulation. *J. Biol. Chem.*, **251,** 844.

Katz, A. M., Repke, D. I., Fudyama, G., and Shigekawa, M. (1977). Control of calcium efflux from sarcoplasmic reticulum vesicles by external calcium. *J. Biol. Chem.*, **252,** 4210.

Keely, S. L., and Eiring, A. (1979). Involvement of cAMP-dependent protein kinase in the regulation of heart contractile force. *Am. J. Physiol.*, **236,** H84.

—— Lincoln, T. M., and Corbin, J. D. (1978). Interaction of acetylcholine and epinephrine on heart cyclic AMP-dependent protein kinase. *Am. J. Physiol.*, **234,** H432.

Kirchberger, M. A., and Wong, D. (1978). Calcium efflux from isolated cardiac sarcoplasmic reticulum. *J. Biol. Chem.*, **253,** 6941.

Kohlhardt, M., and Haap, K. (1978). 8-Bromoguanosine 3′5′ monophosphate mimics the effect of acetylcholine on the slow response, action potential and contractile force in mammalian atrial myocardium. *J. Molec. Cell. Cardiol.*, **10,** 573.

Konno, K. (1978). Two calcium regulatory systems in squid (*Ommastrephes sloani pacificus*) muscle. *J. Biochem. (Tokyo)*, **84**, 1431.

Krebs, E. G., and Beavo, J. A. (1979). Phosphorylation–dephosphorylation of enzymes. *Annu. Rev. Biochem.*, **48**, 923.

Krebs, H. A., Woods, H. F., and Alberti, K. G. M. M. (1975). Hyperlactaemia and lactic acidosis; in *Essays in Medical Biochemistry*, vol. 1 (eds V. Marks and C. N. Hales), p. 81. London: The Biochemical Society.

Kreye, V. A. W. (1978). Organic nitrates, sodium nitroprusside and vasodilatation; in *Mechanisms of Vasodilatation* (eds P. M. Vanhoutte and I. Leusen), p. 158. Basel: S. Karger.

Kuriyama, H., Ito, Y., and Suzuki, H. (1977). Effects of membrane potential on activation and contraction in various smooth muscles; in *Excitation–Contraction Coupling in Smooth Muscle* (eds R. Casteels, T. Godfraind and J. C. Ruegg), p. 25. Amsterdam: Elsevier.

Langer, G. A. (1976). Events at the cardiac sarcolemma: localisation and movement of contractile dependent calcium. *Fed. Proc.*, **35**, 1274.

LaNoue, K. F., and Schoolwerth, A. C. (1979). Metabolite transport in mitochondria. *Annu. Rev. Biochem.*, **48**, 871.

Lebowitz, E. A., and Cooke, R. (1979). Phosphorylation of uterine smooth muscle myosin permits actin activation. *J. Biochem. (Tokyo)*, **85**, 1489.

Lee, S.-H., and Davis, E. J. (1979). Carboxylation and decarboxylation reactions: anaplerotic flux and removal of citrate cycle intermediates in skeletal muscle. *J. Biol. Chem.*, **254**, 420.

Leiber, D., Vesin, M.-F., and Harbon, S. (1978). Regulation of guanosine 3'5' cyclic monophosphate levels and contractility in rat myometrium. *FEBS Lett.*, **86**, 183.

Li, J. B., Higgins, J. E., and Jefferson, L. S. (1979). Changes in protein turnover in skeletal muscle in response to fasting. *Am. J. Physiol.*, **236**, E222.

Limas, C. J. (1978). Enhanced phosphorylation of myocardial sarcoplasmic reticulum in experimental hyperthyroidism. *Am. J. Physiol.*, **234**, H426.

Linke, A., and Betz, E. (1977). NADH level oscillation and oscillatory activity of rat portal vein; in *Excitation–Contraction Coupling in Smooth Muscle* (eds R. Casteels, T. Godfraind and J. C. Ruegg), p. 479. Amsterdam: Elsevier.

Lohmann, S. M., Miech, R. P., and Butcher, F. R. (1977). Effects of isoproterenol, theophylline and carbachol on cyclic nucleotide levels and relaxation of bovine tracheal smooth muscle. *Biochim. Biophys. Acta*, **499**, 238.

Lowenstein, J. M., and Goodman, M. N. (1978). The purine nucleotide cycle in skeletal muscle. *Fed. Proc.*, **37**, 2308.

Ma, T. S., and Bose, D. (1977). Sodium in smooth muscle relaxation. *Am. J. Physiol.*, **232**, C59.

McLane, J. A., and Holloszy, J. O. (1979). Glycogen synthesis from lactate in the three types of skeletal muscle. *J. Biol. Chem.*, **254**, 6548.

MacLennan, D. H., and Wong, P. T. S. (1971). Isolation of a calcium sequestering protein from sarcoplasmic reticulum. *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 1231.

Maizels, E. Z., Ruderman, N. B., Goodman, M. N., and Lau, D. (1977). Effects of acetoacetate on glucose metabolism in the soleus and extensor digitorum longus muscles of the rat. *Biochem. J.*, **162**, 557.

Mannherz, H. G., and Goody, R. S. (1976). Proteins of contractile systems. *Annu. Rev. Biochem.*, **45**, 427.

Mansour, T. E. (1972). Phosphofructokinase. *Curr. Top. Cell. Regul.*, **5**, 1.

Matsushita, S., Sogani, R. K., and Roben, M. S. (1972). Ornithine decarboxylase in cardiac hypertrophy in the rat. *Circ. Res.*, **31**, 699.

Meijer, A. J., and VanDam, K. (1974). The metabolic significance of anion transport in mitochondria. *Biochim. Biophys. Acta*, **346**, 213.

Millward, D. J. (1978). The regulation of muscle protein turnover during growth and development. *Biochem. Soc. Trans.*, **6**, 494.

Moir, A. J. G., and Perry, S. V. (1977). The sites of phosphorylation of rabbit cardiac troponin I by adenosine 3'5' cyclic monophosphate-dependent protein kinase. *Biochem. J.*, **167**, 333.

Morgan, M., Perry, S. V., and Ottoway, J. (1976). Myosin light-chain phosphatase. *Biochem. J.*, **157**, 687.

Mullins, L. J. (1979). The generation of electric currents in cardiac fibres by Na/Ca exchange. *Am. J. Physiol.*, **236**, C103.

Murphy, R. A. (1978). Control of actin–myosin interaction by Ca^{++} in vascular smooth muscle; in *Mechanisms of Vasodilatation* (eds. P. M. Vanhoutte and I. Leusen), p. 30. Basel: S. Karger.

Nayler, W. G. (1975). The cardiac cell; in *Contraction and Relaxation in the Myocardium* (ed. W. G. Naylor), p. 1. London: Academic Press.

Neely, J. R., and Morgan, H. E. (1974). Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle. *Annu. Rev. Physiol.*, **36**, 413.

Newsholme, E. A., Beis, I., Leech, A. R., and Zammit, V. A. (1978). The role of creatine kinase and arginine kinase in muscle. *Biochem. J.*, **172**, 533.

—— Start, C. (1973). *Regulation in Metabolism*, ch. 3, p. 88. London: J. Wiley & Sons.

—— Williams, T. (1978). The role of phosphoenolpyruvate carboxykinase in amino acid metabolism in muscle. *Biochem. J.*, **176**, 623.

Nishiki, K., Erecinska, M., and Wilson, D. F. (1978). Energy relationships between cytosolic metabolism and mitochondrial respiration in rat heart. *Am. J. Physiol.*, **234**, C73.

Nishikori, K., and Maeno, H. (1979). Close relationship between adenosine 3'5' monophosphate-dependent endogenous phosphorylation of a specific protein and stimulation of calcium uptake in rat uterine microsomes. *J. Biol. Chem.*, **254**, 6099.

Odessey, R., and Goldberg, A. L. (1979). Leucine degradation by cell-free extracts of skeletal muscle. *Biochem. J.*, **178**, 475.

Parker, P. J., and Randle, P. J. (1978). Inactivation of rat heart branched chain 2-oxoacid dehydrogenase complex by adenosine triphosphate. *FEBS Lett.*, **95**, 153.

Perry, S. V. (1952). The bound nucleotide of the isolated myofibril. *Biochem. J.*, **51**, 495.

—— (1975). The contractile and regulatory proteins of the myocardium; in *Contraction and Relaxation in the Myocardium* (ed. W. G. Naylor), p. 29. London: Academic Press.

Perry, S. V. (1979). The regulation of contractile activity in muscle. *Biochem. Soc. Trans.*, **7,** 593.

—— Grand, R. J. A., Nairn, A. C., Vanaman, T. C., and Wall, C. M. (1979). Calcium binding proteins and the regulation of contractile activity. *Biochem. Soc. Trans.*, **7,** 619.

Peter, J. B., Barnard, R. J., Edgerton, V. R., Gillespie, C. A., and Stempel, K. E. (1972). Metabolic profiles of three fibre types in guinea pigs and rabbits. *Biochemistry*, **11,** 2627.

Pette, D., and Dolken, G. (1974). Some aspects of regulation of enzyme levels in muscle energy-supplying metabolism. *Adv. Enzyme Regul.*, **13,** 355.

—— Schnez, U. (1977). Coexistence of fast and slow myosin light chains in single muscle fibres during transformation as induced by long-term stimulation. *FEBS Lett.*, **83,** 128.

Pires, E. M. V., and Perry, S. V. (1977). Purification and properties of myosin light-chain kinase from fast skeletal muscle. *Biochem. J.*, **167,** 137.

Pitts, B. J. R. (1979). Stoichiometry of sodium–calcium exchange in cardiac sarcolemmal vesicles. *J. Biol. Chem.*, **254,** 6232.

Potter, J. D. (1974). The content of troponin, tropomyosin, actin and myosin in rabbit skeletal muscle myofibrils. *Arch. Biochem. Biophys.*, **162,** 436.

Ramaiah, A. (1976). Regulation of glycolysis in skeletal muscle. *Life Sci.*, **19,** 455.

Ray, K. P., and England, P. J. (1976). Phosphorylation of the inhibitory subunit of troponin and its effect on the calcium dependence of cardiac myofibril adenosine triphosphatase. *FEBS Lett.*, **70,** 11.

Rennie, M. J., and Holloszy, J. O. (1977). Inhibition of glucose uptake and glycogenolysis by availability of oleate in well oxygenated perfused skeletal muscle. *Biochem. J.*, **168,** 161.

Reuter, H., and Scholz, H. (1977). The regulation of the calcium conductance of cardiac muscle by adrenalin. *J. Physiol. (Lond.)*, **264,** 49.

Rieser, G., Sabbani, R., Paolini, P., Fry, M., and Inesi, G. (1979). Sarcomere motion in isolated cardiac cells. *Am. J. Physiol.*, **236,** C70.

Roy, M. K., Mabuchi, K., Sarkar, S., Mis, C., and Sreter, F. A. (1979). Changes in tropomyosin subunit pattern in chronically electrically stimulated rabbit fast muscles. *Biochem. Biophys., Res. Commun.*, **89,** 181.

Saks, V. A., Rosenshtraukh, L. V., Smirnov, V. N., and Chazov, E. I. (1978). Role of creatine phosphokinase in cellular function and metabolism. *Can. J. Physiol. Pharmacol.*, **56,** 691.

Sanchez, J. A., and Stefani, E. (1978). Inward calcium current in twitch muscle fibres of the frog. *J. Physiol. (Lond.)*, **283,** 197.

Sarkar, S., Sreter, F. A., and Gergely, J. (1971). Light chains of myosins from white, red and cardiac muscles. *Proc. Natl. Acad. Sci. U.S.A.*, **68,** 946.

Schiff, J. D., and Overweg, N. I. A. (1978). Cyclic AMP independent relaxation of depolarized rat ileal smooth muscle by isoproterenol. *Life Sci.*, **23,** 2299.

Schliselfeld, L. H., Davis, C. H., and Krebs, E. G. (1970). A comparison of phosphorylase isoenzymes in the rabbit. *Biochemistry*, **9,** 4959.

Schoenberg, C. F., and Needham, D. M. (1976). A study of the mechanism of contraction in vertebrate smooth muscle. *Biol. Rev.*, **51,** 53.

Schulz, K. D., Schulz, K., and Schulz, G. (1977). Sodium nitroprusside and other smooth muscle relaxants increase cyclic GMP in rat ductus deferens. *Nature (Lond.)*, **265,** 750.

Sharma, V. K., and Banerjee, S. P. (1978). α-Adrenergic receptor in rat heart: effects of thyroidectomy. *J. Biol. Chem.*, **253,** 5277.

Shoji, M., Brackett, N. L., Tse, J., Shapira, R., and Kuo, J. F. (1978). Molecular properties and mode of action of homogeneous preparation of stimulatory modulator of cyclic GMP-dependent protein kinase from the heart. *J. Biol. Chem.*, **253,** 3427.

Shoji, S., and Pennington, R. J. T. (1977). The effect of cortisone on protein synthesis and breakdown in rat skeletal muscle. *Molec. Cell. Endocrinol.*, **6,** 159.

Shorr, R. G., Dolly, J. O., and Barnard, E. A. (1978). Composition of acetylcholine receptor from skeletal muscle. *Nature (Lond.)*, **274,** 283.

Siegel, G., Ehehalt, R., and Koepchen, H. P. (1978). Membrane potential and relaxation in vascular smooth muscle; in *Mechanisms of Vasodilatation* (eds P. M. Vanhoutte and I. Leusen), p. 56. Basel: S. Karger.

Singh, J., Flitney, F. W., and Lamb, J. F. (1978). Effects of isoprenaline on contractile force and intracellular cyclic 3′5′ nucleotide levels in the hypodynamic frog ventricle. *FEBS Lett.*, **91,** 269.

Snell, K., and Duff, D. A. (1977). The release of alanine by diaphragm muscle *in vivo*. *Biochem. J.*, **162,** 399.

Somlyo, A. P., and Somlyo, A. V. (1976). Ultrastructural aspects of activation and contraction in vascular smooth muscle. *Fed. Proc.*, **35,** 1288.

Somlyo, A. V. (1978). The contractile apparatus of vascular smooth muscle; in *Mechanisms of Vasodilatation* (eds P. M. Vanhoutte and I. Leusen), p. 12. Basel: S. Karger.

Stone, D., and Smillie, L. B. (1978). The amino acid sequence of rabbit skeletal muscle α-troponin. *J. Biol. Chem.*, **253,** 1137.

Sugden, P. H., Hutson, N. J., Kerbey, A. L., and Randle, P. J. (1978). Phosphorylation of additional sites on pyruvate dehydrogenase inhibits its reactivation by pyruvate dehydrogenase phosphate phosphatase. *Biochem. J.*, **169,** 433.

Suzuki, H., Onishi, H., Takahashi, K., and Watanabe, S. (1978). Structure and function of chicken gizzard myosin. *J. Biochem. (Tokyo)*, **84,** 1529.

Tada, M., Ohmori, F., Yamada, M., and Abe, H. (1979). Mechanism of stimulation of Ca^{++}-dependent ATPase of cardiac sarcoplasmic reticulum by adenosine 3′5′ monophosphate-dependent protein kinase. *J. Biol. Chem.*, **254,** 319.

—— Yamamoto, T., and Tonomura, Y. (1978). Molecular mechanism of active calcium transport by sarcoplasmic reticulum. *Physiol. Rev.*, **58,** 1.

Tomas, F. M., Munro, H. N., and Young, V. R. (1979). Effect of glucocorticoid administration on the rate of muscle protein breakdown *in vivo* in rats, as measured by the excretion of N-methyl histidine. *Biochem. J.*, **178,** 139.

Trentham, D. R. (1977). The adenosine triphosphatase reactions of myosin and actomyosin and their relationship to energy transduction in muscle. *Biochem. Soc. Trans.*, **5**, 5.

Tsukui, R., and Ebashi, S. (1973). Cardiac troponin. *J. Biochem.* (*Tokyo*), **73**, 1119.

Twarog, B. M. (1976). Aspects of smooth muscle function in molluscan catch muscle. *Physiol. Rev.*, **56**, 829.

Veech, R. L., Lawson, J. W. R., Cornell, N. W., and Krebs, H. A. (1979). Cytosolic phosphorylation potential. *J. Biol. Chem.*, **254**, 6538.

Watanabe, A. M., and Besch, H. R. (1975). Interaction between cyclic adenosine monophosphate and cyclic guanosine monophosphate in guinea pig ventricular myocardium. *Circ. Res.*, **37**, 309.

—— Hathaway, D. R., Besch, H. R., Farmer, B. B., and Harris, R. A. (1977). α-Adrenergic reduction of cyclic adenosine monophosphate concentrations in rat myocardium. *Circ. Res.*, **40**, 596.

Watkinson, W. P., Foley, D. H., Rubio, R., and Berne, R. M. (1979). Myocardial adenosine formation with increased cardiac performance in the dog. *Am. J. Physiol.*, **236**, H13.

Weber, A., and Murray, J. M. (1973). Molecular control mechanisms in muscle contraction. *Physiol. Rev.*, **53**, 612.

Weeds, A. G., and Burridge, K. (1975). Myosin from cross-reinnervated cat muscles. Evidence for the reciprocal transformation of heavy chains. *FEBS Lett.*, **57**, 203.

Wendt, I. R., and Langer, G. A. (1977). The sodium–calcium relationship in mammalian myocardium. Effects of sodium deficient perfusion on calcium fluxes. *J. Molec. Cell. Cardiol.*, **9**, 551.

Williams, L. T., Lefkowitz, R. J., Watanabe, A. M., Hathaway, D. R., and Besch, H. R. (1977). Thyroid hormone regulation of β-adrenergic receptor number. *J. Biol. Chem.*, **252**, 2787.

Winstanley, M. A., Trayer, H. R., and Trayer, I. P. (1977). Role of myosin light chains in binding to actin. *FEBS Lett.*, **77**, 239.

Yagi, K., Yazawa, M., Kakiuchi, S., Ohshima, M., and Uenishi, K. (1978). Identification of an activator protein for myosin light chain kinase as the Ca^{++}-dependent modulator protein. *J. Biol. Chem.*, **253**, 1338.

Zierler, K. L. (1976). Fatty acids as substrates for heart and skeletal muscle. *Circ. Res.*, **38**, 459.

Br. J. Anaesth. (1980), **52**, 139

PATHOLOGY OF MUSCLE

P. H. Buxton

Voluntary muscle is not only activated by nervous impulses, but it is also highly dependent on the trophic action of an intact nerve supply to maintain a normal healthy state. It is therefore important when considering diseases of muscle to consider also diseases affecting its innervation, since breakdown can occur at many different stages between the nervous system and the final motor response. A brief summary of neuromuscular activation is therefore given before describing the effects on muscle of disease at these different stages.

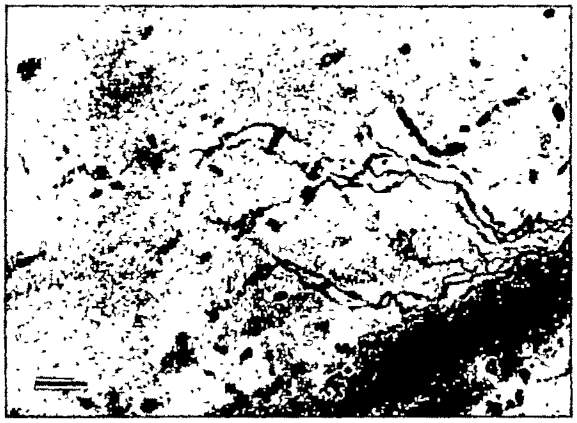


Fig. 1. Intravital methylene blue stain to show subterminal nerve fibres and end-plates on muscle fibres. Bar = 50 μm.

When a voluntary muscle contracts, the impulse initiated by the cortex stimulates an anterior horn cell which sends an impulse via a motor nerve fibre to the evoked muscle. On reaching this muscle the nerve fibre divides into several smaller branches which further subdivide near their destination into the terminal motor fibres, each of which ends on a single muscle fibre where it forms a group of terminal expansions—the motor end-plate (fig. 1). Thus, through the branching of the original anterior horn cell nerve fibre, several groups of end-plates may be activated simultaneously; this group is known as the motor-unit.

At the motor end-plate the small electrical nervous impulse releases the intermediate chemical transmitter acetylcholine (ACh) which diffuses across the synaptic membrane and attaches to the post-synaptic receptors on the muscle membrane; when a critical amount of ACh is fixed, depolarization of the muscle fibre membrane occurs and an action potential arises; any surplus ACh is removed by the enzyme cholinesterase and the choline is recycled. The action potential is rapidly transmitted to all the contractile elements of the muscle—the myofibrils—by the sarcotubular system and contraction takes place by the thin actin fibrils sliding between the thicker myosin fibrils, regulated by tropomyosin and troponin. The intensity of contraction of the muscle by the recruitment of motor units is controlled by nervous impulses from the muscle spindles and sensors in the joints and ligaments.

The nervous impulses for initiation and control and the muscular contraction itself require energy, fuel for which must be brought by the blood stream to the site where it is required, and metabolites must be rapidly removed. The form of energy used is adenosine triphosphate (ATP) which is produced in muscle by the aerobic metabolism of glucose and fatty acids in mitochondria; type I, the red, slow-twitch muscle fibres, are rich in these oxidative enzymes. ATP may also be produced by the anaerobic breakdown of muscle glycogen which requires the enzyme myophosphorylase; type II, the white, fast-twitch muscle fibres are rich in this enzyme. All human muscles have a mixture of these two fibre types, which can be differentiated by histochemical staining of cryostat sections from muscle biopsy. In practice, fibre type differentiation is done by staining for ATPase at pH 9.4 after preincubation of the cryostat sections at acid pH when type I fibres stain, or at alkaline pH when type II fibres stain (Dubowitz and Brooke, 1973) (fig. 2).

When considering pathology of the neuromuscular system, the terms neurogenic atrophy or

---

P. H. Buxton, M.D., F.R.C.P., F.R.C.Path., Neuropathology Laboratory, Walton Hospital, Rice Lane, Liverpool L9 1AE.

0007–0912/80/020139–13 $01.00

© Macmillan Journals Ltd 1980

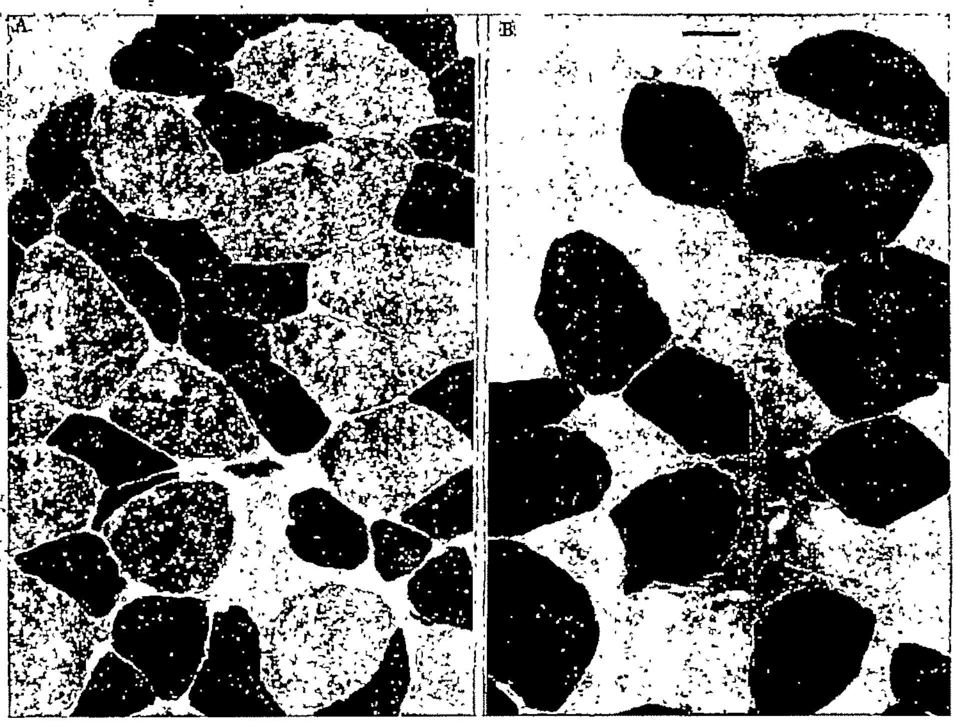


FIG. 2. A: ATPase at pH 9.4 to show darkly staining type II muscle fibres. B: ATPase after preincubation at pH 4.3 to show darkly-staining type I muscle fibres. A and B show the complementary staining. Bar = 50 μm.

neuromyopathy are often used to describe the changes in muscle tissue resulting from disease of neural origin such as denervation, whereas myopathy is usually restricted to diseases principally affecting muscle tissue itself. Myopathy may be further subdivided into primary myopathy, where the pathological process appears to arise in muscle, and secondary myopathy, where muscle tissue is affected by factors outside the neuromuscular system.

NEUROMYOPATHY

Denervation

Complete transection of a peripheral motor nerve causes complete flaccid paralysis of the muscle it innervates and these muscle fibres rapidly atrophy. The myofibrils on the periphery of the muscle fibre disintegrate so that groups of thin fibres with faint myofibrillar striations remain and the sarcolemmal nuclei lie closer together. In 60 days denervated muscle shows a 70% reduction of fibre area (Sunderland, 1968) compared with a 20% loss in disuse atrophy. While striations persist, reinnervation is possible, and if this occurs muscle fibres recover their activity and bulk; if reinnervation does not take place the muscle fibres eventually degenerate and fibrous tissue or fat may partially replace them.

More usually, denervation is partial as in the polyneuropathies or when an anterior horn cell is damaged as by poliomyelitis, progressive spinal muscular atrophy or in motor neurone disease. Paralysis then occurs in the muscle fibres in the motor unit activated by the damaged anterior horn cell. Changes occur rapidly in these denervated fibres; they shrink so that their sarcolemmal nuclei appear to be more numerous and adjacent muscle fibres in the same fasciculus innervated by other undamaged anterior horn cells appear normal in size or even show slight hypertrophy to compensate for the paralysed fibres.

The denervated muscle fibres evoke a response from neighbouring healthy nerve fibres which send out fine filaments to the denervated muscle fibres to reinnervate them. This is called "terminal sprouting" (fig. 3) and can be demonstrated by "motor-point" biopsy (Harriman, 1961). Another characteristic feature of denervation arises because all the denervated muscle fibres in the vicinity of a surviving nerve will be reinnervated by the sprouting twigs from this same nerve. Such muscle fibres will all

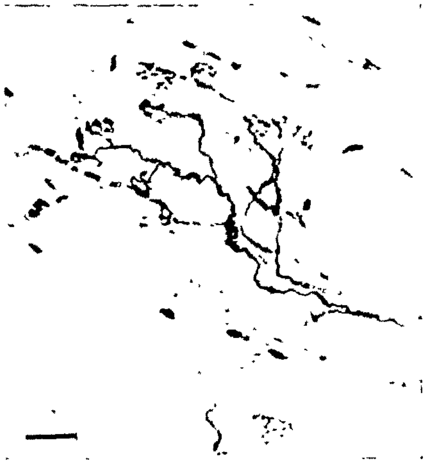


FIG. 3. Methylene blue stain to show branching "sprouting" of terminal nerve fibres. Bar = 50 µm.

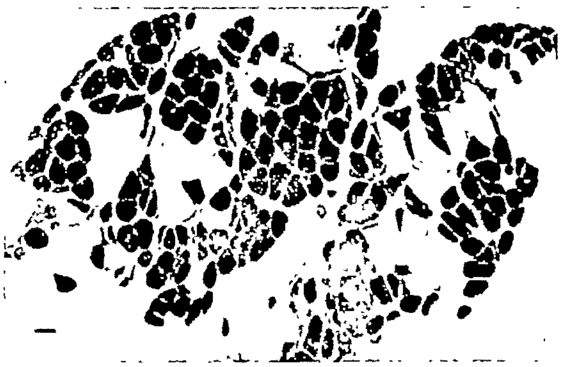


FIG. 4. ATPase preincubated at pH 4.3. To show grouping of muscle fibre types. Bar = 50 µm.

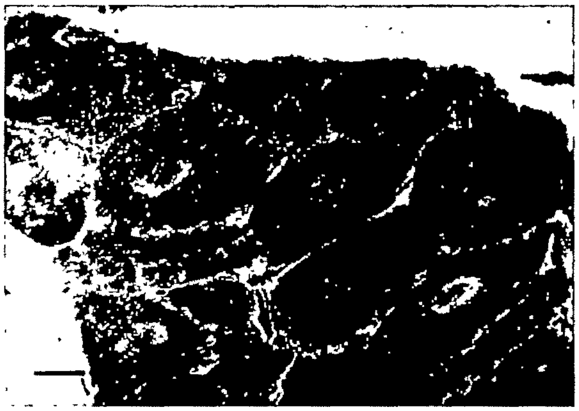


FIG. 5. "Target" fibres. PTAH. Bar = 50 µm.

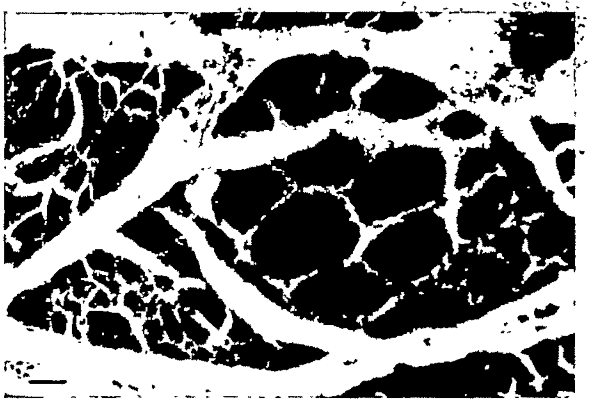


FIG. 6. Denervation. To show normal and small muscle fibres, scattered and in groups. Haematoxylin and eosin. Bar = 50 µm.

assume the same metabolic "type" since this is determined by the anterior horn cell innervation. Histochemical staining of frozen sections from muscle biopsy will show this grouping of fibre types which is pathognomonic of reinnervation (fig. 4).

Another abnormality seen in histochemical stains in certain cases of denervation, particularly in cases of recovering polyneuritis (Harriman, 1976), are "target fibres" (fig. 5) so called because of the three concentric zones (Engel, 1961). Cross-sections of such fibres show a central zone devoid of enzyme activity and an intermediate zone where such activity is more intense. These findings are explained by electron microscopy which shows absence of mitochondria from centrally placed disorganized myofibrillar material, but increased numbers of mitochondria in the intermediate zones.

In summary, the characteristic features of denervation change as seen on muscle biopsy are: large groups of small muscle fibres with increased numbers of sarcolemmal nuclei, usually with some residual normal muscle fibres (fig. 6); terminal sprouting of nerve fibres; and muscle fibre type grouping.

Genetic Neuropathy

Spinal muscular atrophy (SMA)

Genetically determined SMA is now usually divided into three categories. All are transmitted by autosomal recessive inheritance with occasional sporadic cases.

Werdnig Hoffman (WH) disease is the most severe form. There is progressive weakness and wasting of muscles at or shortly after birth. Mothers of such children may have noticed reduction in fetal movements a few months before birth. The affected baby is hypotonic and immobile yet alert. The cranial nerves can be affected, the cry is weak and fasciculation of the tongue may be seen. Most of these babies die within the first year.

Biopsy shows groups of small atrophied muscle fibres with other groups of normal or even hypertrophied fibres supplied by as yet unaffected anterior horn cells. Terminal nerve "sprouting" or fibre type grouping may be seen before the disease is too advanced.

At postmortem the anterior horn cells at all levels show degenerative changes, from ballooning when chromatolysis is severe, to pyknotic shrinkage and neuronophagia. Reactive gliosis later occurs in the anterior horns and this is well seen in sections stained by Holzer's stain. The anterior nerve roots appear thin and contrast plainly with the normal posterior roots. The cranial nerve motor nuclei may be affected, but the Betz cells are not.

A milder form of WH. The onset is usually between 6 months and 1 year; the child is unable to walk and scoliosis is common. The legs are affected more than the arms. Weakness tends not to progress, but if intercostals are affected prognosis is worse, because of respiratory infections. Changes in muscle at biopsy are similar to although less severe than those in WH.

Kugelberg–Welander (KW) syndrome (Kugelberg and Welander, 1956) is the mildest form of SMA. The proximal muscles, mainly of the lower limbs, are worst affected; the course is usually benign, although slow progression may occur. Clinically and pathologically differential diagnosis from Limb Girdle dystrophy may be difficult in juvenile cases as there may be a moderate increase in serum CPK concentrations in both conditions. Biopsy may show central nuclei, muscle fibre size variation, fibre splitting, necrosis and regeneration, all suggestive of dystrophy. However, terminal nerve sprouting may be seen at motor point biopsy and fibre type grouping found by histochemical stains; these are pathognomonic changes of attempted reinnervation after denervation. In adult cases the denervation changes are often more apparent with groups of small muscle fibres with increased numbers of sarcolemmal nuclei.

Motor Neurone Disease

Motor neurone disease (MND) is the term applied in this country to a relentlessly progressive disease affecting upper and lower motor neurons. In the U.S.A. and on the Continent the term amyotrophic lateral sclerosis (ALS) has often been used. The disease is usually sporadic, although familial cases do occur. Muscles supplied by the affected neurones are weak and wasted, despite brisk reflexes. Extraocular muscles are not involved, but bulbar muscles often are. When the disease process is advancing and destroying the anterior horn cells innervating a muscle, that muscle may show fasciculation which can be recorded by the electromyograph.

In the active stage of the disease the serum creatine kinase may be moderately increased and it is this finding that often leads to a request for muscle biopsy to exclude the more benign Limb Girdle dystrophy or treatable polymyositis. Biopsy usually shows clear-cut evidence of denervation (fig. 6)—groups of small atrophic muscle fibres, terminal sprouting, fibre type grouping—but in the early stages necrosis and regeneration of muscle fibres are occasionally seen.

Myasthenia Gravis (MG)

Patients suffering from this condition have progressive weakness following repetitive muscular contraction or sustained tension, this weakness recovering after a period of rest. A diagnostic test for MG shows a decrease in the action potential following repetitive supramaximal stimuli.

In 1934 Mary Walker showed that treatment with the anticholinesterase drug physostigmine could improve muscle strength in MG. The injection of a small dose of edrophonium (Tensilon) has become a routine outpatient screening test for MG.

It is now thought that reduction in the available number of acetylcholine receptors (AChR) in the secondary synaptic folds is the cause of the symptoms. The action of anticholinesterase drugs by prolonging the action of available ACh gives more opportunity for ACh to become attached to the reduced numbers of viable receptors. The actual damage to the AChR is thought to be a result of an autoimmune process, probably associated with the thymus. In a recent personal view of the pathogenesis of MG, Simpson (1978) made the interesting speculation that an immunological mechanism might be used in the normal animal as the homeostatic device for detecting and removing effete and degenerating tissues. He further speculates that, possibly, the thymus also plays a role in promoting regeneration, so that if we could isolate the factor responsible for active regenerative activity of damaged motor nerve terminals, we would perhaps have the ultimate therapy for MG.

Antibody to human muscle AChR has been measured by a radioimmunoassay technique (Lindstrom et al., 1976). Significantly greater amounts of antibody were found in the serum of MG patients compared with normal subjects, although patients suffering from the Eaton–Lambert syndrome (a myasthenic syndrome associated with malignant disease) did not show a similar increase in antibody to AChR.

Despite the clear-cut symptoms, little abnormality is usually seen at muscle biopsy. The classic feature, collections of "lymphorrhages" (groups of lymphocytes and plasma cells between the muscle fibres), is, in our experience, rarely seen, but abnormality of the motor end-plates may be seen at motor point biopsy. Elongation of the end-plate (fig. 7), often with distal subterminal sprouting from the terminal expansions, is the suggestive feature, although seldom are these changes on their own sufficiently clear cut to be diagnostic. Electron microscopy of the end-plate shows short, stumpy secondary post-synaptic folds. These morphological changes at the end-plate are also seen in the myasthenic malignancy syndrome, but have not been described in other neuromuscular conditions.

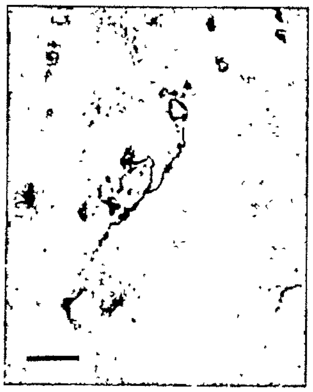


FIG. 7. Myasthenia gravis. Intravital methylene blue, to show elongation of motor end-plate. Bar = 50 µm.

In long standing MG secondary denervation changes may take place in affected muscles.

Familial Periodic Paralysis

Changes in the muscle membrane and sarcotubular system with changes in serum potassium concentration are thought to be responsible for familial periodic paralysis in all three forms of the disease—hypo-, hyper- and normokalaemic.

The hypokalaemic form occurs as an autosomal dominant familial disorder. Attacks usually begin in the second decade and affect the limbs, but usually spare speech, swallowing and respiration. They often start early in the morning, may follow rest after exercise or may be precipitated by a heavy carbohydrate meal. The attacks may be ended by further exercise or by administration of potassium salts. Some permanent weakness may follow repeated attacks.

Hypokalaemia may also occur in hyperaldosteronism, during insulin treatment of diabetic coma, and diuretic treatment if no potassium supplements are given. Similar attacks of hypokalaemic paralysis are reported in cases of thyrotoxicosis, particularly in patients of oriental origin.

Hyperkalaemic periodic paralysis is also inherited as an autosomal dominant trait. Attacks often follow exercise, they may last for 1 or 2 hours and may be controlled by calcium gluconate or by insulin with glucose. There is often an association with mild myotonia. As in hypokalaemia, muscle strength is normal between attacks, but recurrent attacks can produce permanent weakness.

Normokalaemic periodic paralysis is rare. Attacks are similar to those of hyperkalaemia, but may last much longer.

Histologically, the characteristic finding in all these periodic paralyses is vacuole formation within muscle fibres. The vacuoles, some of which contain glycogen, may be seen by the light microscope in cryostat sections at routine muscle biopsy, but they are better seen by electron microscopy, when they appear in the membranes of the sarcoplasmic reticulum or in the dilated terminal cisterns of the triads. In long standing cases muscle fibres may show necrosis and regeneration with variation in fibre size and increased fibrosis.

PRIMARY MYOPATHIES

The Genetic Dystrophies

Duchenne muscular dystrophy (*DMD*) is a severe, progressive muscle disease of boys, affecting particularly the thigh and pelvic muscle, although few voluntary muscles except the extraocular muscles are unaffected. The disease is usually first apparent at 4 or 5 years; the child tends to fall at play, has difficulty climbing stairs and difficulty getting up from the floor, when he may have to use his hands and arms to climb up to his knees—Gower's sign. Progression of the disease is relentless, most cases are confined to a wheel chair by their 'teens and few survive into the third decade.

Inheritance is by the X-linked recessive mode. All cases and 70% of carriers have increased serum creatine phosphokinase (CPK) concentrations. The younger such female carriers are when their serum is tested, the more likely are they to show abnormal concentrations. Recently, estimation of serum myoglobin has been shown to be a useful adjunct in the detection of carriers of DMD (Adornato, Kagen and King Engel, 1978).

The main pathological changes are a progressive diminution in total numbers of muscle fibres and necrosis of single fibres, parts of a fibre and groups of fibres. The necrosis is associated with regeneration in the earlier stages. Thus phagocytosis, variation in muscle fibre size, centrally placed sarcolemmal nuclei, sarcoplasmic basophilia and increased endomysial fat and fibrous tissue are typical findings at biopsy (fig. 8). The serum enzyme CPK has been found to be the most specific indicator of muscle disease in DMD, the concentration being markedly increased, particularly in the early stages.

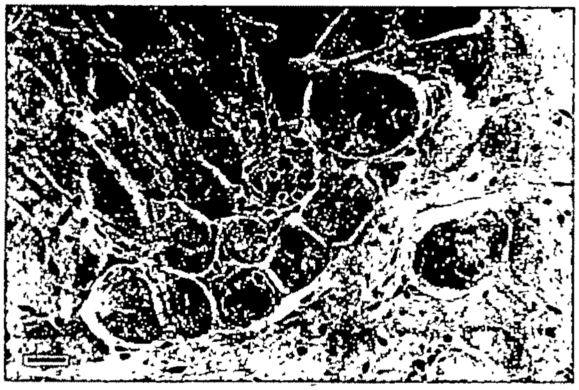


FIG. 8. Duchenne dystrophy to show variation in muscle fibre size, central nuclei, bands of collagen. Haematoxylin and eosin. Bar = 50 µm.

Although the pathological process has always been thought to involve primarily the muscle cell itself, it should be remembered that other tissues are usually involved. Many cases have tachycardia, the e.c.g. is often abnormal and abnormalities may be found in the myocardium. The central nervous system is often affected, as shown by a reduction in the average I.Q. of these patients.

Many theories concerning pathogenesis have been postulated. The "vascular theory" (Engel, 1974) considered whether the tendency to clustering of degenerate fibres and the marked interstitial fibrosis in DMD could be a result of recurrent episodes of local ischaemia of muscle. The "neural" "sick motor neurone" theory (McComas et al., 1976) considered whether reduction in numbers of functioning motor units found in some dystrophic muscles is the cause of DMD.

Certainly the characteristic pathological feature consistently found by the light microscope is segmental necrosis of muscle fibres. At electron microscopy there have been many reports of plasma membrane defects, but whether such membrane defects are the primary abnormality in DMD is still undecided.

Becker-type muscular dystrophy (*BMD*) is a more slowly progressive X-linked disease of muscle with a later onset than DMD and with a longer life expectancy. All cases show increased serum c.p.k. concentrations, particularly in the early stages of the disease.

In a recent clinical, physiological, pathological review of eight families, Bradley, Jones and Fawcett (1978) found that all but one of the patients were still able to walk at 16 years of age and most lived beyond 20 years. First symptoms usually arose around 10 years, rarely after 25. Proximal lower limb muscles were affected early and were always most severely involved. Hypertrophy or pseudohypertrophy of muscles, especially the calves, was very frequently found.

Pathologically, variation in muscle fibre size with many atrophic and some hypertrophic fibres was the commonest finding. Multiple internal nuclei and endomysial fibrosis were often seen, but also many clumps of pyknotic nuclei and split and angulated fibres, more suggestive of denervation. Necrosis, phagocytosis and regeneration were also common.

Thus, many of the pathological findings are similar to the changes in milder DMD, yet the striking feature of these cases is the finding of denervation changes as well as myopathic change often in the same family. Bradley's group therefore suggests that, in BMD, the genetic disorder is expressed both in the muscle and in the motor innervation.

Limb girdle dystrophy (*LGD*) is the term used for a progressive weakness affecting predominantly the pelvi–femoral proximal muscles or, rather less commonly, the scapulo–humeral muscles. Inheritance is autosomal recessive which differentiates Becker dystrophy in females, although differentiation from BMD may be difficult in males. Many cases arise sporadically.

The age of onset is extremely variable, from childhood to adult life, most cases beginning in the second or third decade. Progression of the disease is usually slow and the symptoms resemble BMD rather than DMD. Because of the variability of the clinical picture, confusion with benign spinal muscular atrophy or other neurogenic disease may arise.

In LGD, serum CPK concentration is usually increased, but often only mildly. Histologically, great variation in muscle fibre size with frequent muscle fibre splitting is seen and ring fibres may be found (fig. 9). Many muscle fibres have central nuclei; but necrosis, basophilia and increased fibrosis are infrequent.

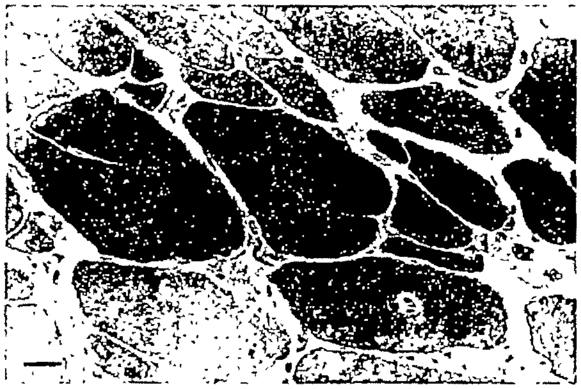


FIG. 9. Limb girdle dystrophy to show variation in fibre size, central nuclei, muscle fibre splitting. Haematoxylin and eosin. Bar = 50 μm.

Weakness confined to the quadriceps has been described and such cases are thought to be a *forme fruste* of LGD (Walton and Gardner-Medwin, 1974).

Facio–scapulo–humeral dystrophy (*FSH*) is a relatively uncommon form of dystrophy; inheritance is autosomal dominant, but shows much variation in severity within families. Thus patients markedly affected may have relatives with mild facial weakness only.

The disease usually begins in the second or third decade, but when, unusually, it starts in childhood the disability is often severe. The facial muscles are usually involved first, then the scapulo–humeral group. The anterior tibial group of muscles may also be involved and later the muscles around the hip. The mode of inheritance and involvement of the facial muscles differentiate this form of dystrophy from the limb girdle type. Progression of the disease is slow and, although patients may be disabled, life expectancy is not grossly curtailed.

Serum CPK concentration may be normal or only slightly increased. Histologically, there is variation in muscle fibre size with the average size tending to be rather large. However, some small angulated fibres are often seen and these have been interpreted as evidence of neurogenic change by some, although fibre-type grouping is not a feature in histochemical stains. Internal nuclei are not often found in this dystrophy nor is fibrosis, yet an unusual feature of the disease is finding groups of inflammatory cells in a number of cases (Dubowitz and Brooke, 1973).

Polymyositis is an inflammatory disease of muscle considered to be caused by an autoimmune disturbance, probably a delayed hypersensitivity reaction mediated by sensitized lymphocytes or plasma cells. It is of very great practical importance because, although it may present in many different ways, it is a treatable condition. The clinical classification of polymyositis (Walton and Adams, 1958) is still very convenient and a guide to prognosis:

Group 1	Pure polymyositis
Group 2	Polymyositis with some evidence of collagen vascular disease
Group 3	Collagen vascular disease complicated by polymyositis
Group 4	Polymyositis in association with malignant disease

Clinically, polymyositis presents with muscular weakness, progressive over 3–12 months; occasionally it may present acutely over a few days or weeks and is then occasionally associated with myoglobinuria. In the more chronic form it may be clinically indistinguishable from a muscular dystrophy. The weakness is usually proximal, although distal muscles may be affected. Affected muscles may be tender; weakness of neck muscles and dysphagia are seen in some cases. The disease can occur at any age, but the majority of cases occur after 30 years. Females are affected more frequently than males (approx. 3 : 2).

Serum CPK concentration is increased in 60% of cases and the ESR is increased in about 60% also. Electrophoresis may show an increase in immunoglobulins and, if associated with collagen vascular disease, antinuclear factor, LE cells and eosinophilia may be found.

As the disease process is often patchy in distribution, it is important to select for biopsy a muscle that is affected but not too severely; ideally a tender muscle showing slight weakness is chosen. Even in such a muscle, there will be a wide variety of reactive and reparative cellular changes. Destruction of segments of single fibres may be found, often those on the periphery of fasciculi. Phagocytosis and regeneration are seen and sometimes vacuolation, particularly in cases associated with collagen vascular disease. It is, however, the aggregates of inflammatory cells, lymphocytes, plasma cells and histiocytes, lying between muscle fibres and around blood vessels, that are characteristic of this condition.

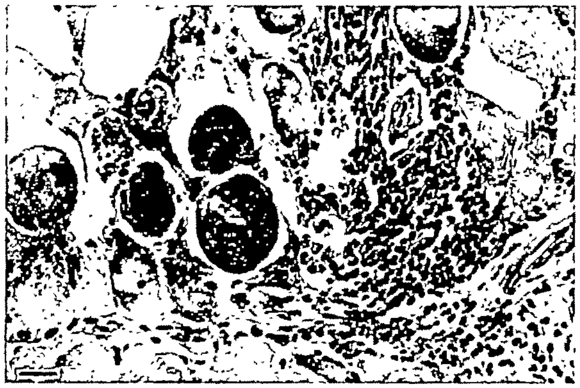


FIG. 10. Myositis to show inflammatory cells, variation in muscle fibre size, central nuclei. Haematoxylin and eosin. Bar = 50 µm.

These pathological changes are similar in all groups in the Walton–Adams classification, although the changes in interstitial tissue are more marked in groups 2, 3 and 4.

There is considerable variation in different series as to the frequency of malignant disease in polymyositis. De Vere and Bradley (1975) found only 8%, whilst others report up to 25%. However, in patients with dermatomyositis who are older than 40 years, the frequency of malignant disease increases to 40% in females, and more than 60% in males. Even in group 4 cases, diagnosis is important because polymyositis may arise at a very early stage in the development of the malignancy, with a prospect of cure and subsidence of the symptoms of polymyositis if the tumour is removed.

Myotonic Dystrophy

In this condition patients show myotonia, weakness and wasting of muscles. Inheritance is by an autosomal dominant trait, but there may be marked variation in severity within a family. The disease is usually first noted in early adult life although it may start in childhood. There is difficulty in relaxing muscles, for example after shaking hands, and a slowly progressive distal muscle weakness. Facial weakness, ptosis, wasting of masseters and temporalis give a characteristic appearance. In addition, as the disease progresses frontal baldness, cataracts, gonadal atrophy and cardiac conduction defects arise, so that many of these patients have a severe handicap in later adult life.

E.m.g., acoustically, gives the diagnostic "dive bomber" effect, from spontaneous bursts of high amplitude potentials with gradual decrement. Serum CPK concentrations may be normal or slightly increased. Histological changes are very characteristic; a high percentage of muscle fibres have central nuclei and on longitudinal section these are often seen as chains of nuclei (fig. 11). There is variation in fibre size, type I fibres tending to be small and type II large; ring fibres are often seen. Small angular fibres may be found in the later stages of the disease, an appearance suggestive of denervation. Muscle spindles in this condition may show increased numbers of intrafusal fibres and motor end-plates shown at motor point biopsy are often enlarged. Eventually

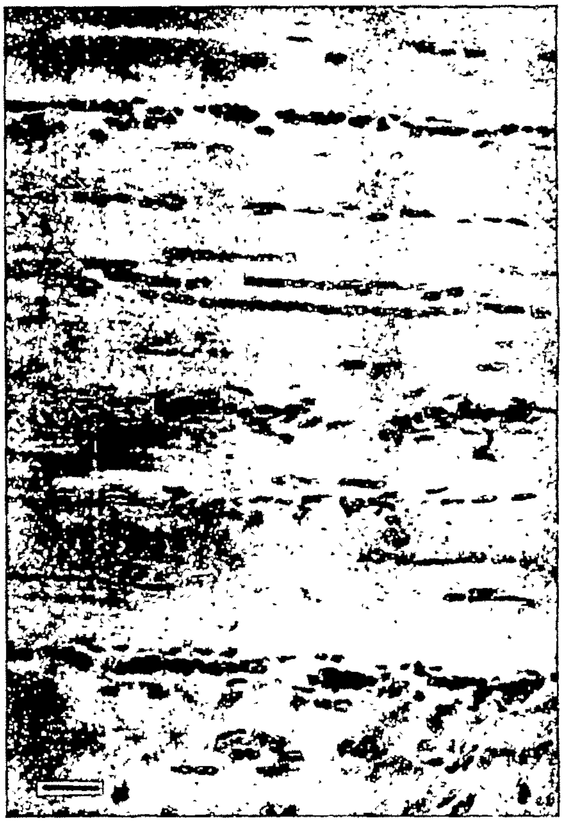


FIG. 11. Myotonic dystrophy to show chains of sarcolemmal nuclei. Haematoxylin and eosin. Bar = 50 µm.

necrosis, phagocytosis and fibrosis reaffirm the myopathic changes.

Myotonia Congenita (MC)

Thomsen originally described this disease in his own family, in which it was inherited by the autosomal dominant mode; Becker (1971) differentiated an autosomal recessive form of the disease. Kuhn and others (1979) have recently summarized the relevant data in a 70th birthday tribute to Professor Becker. Clinically, the two forms of MC are not distinguishable in any single case, although the recessive tends to be more severe, most cases starting between 4 and 12 years of age. Myotonia is often first noted in the legs, but the tongue and muscles of mastication are frequently affected. The myotonia may be associated with muscle weakness. Hypertrophy of the glutei, thighs, calves and shoulders is often seen in males with the autosomal recessive form of the disease; abnormal firmness of the muscles and limited extension of the wrist is also a feature of this form. Generally, myotonia congenita is a considerably milder condition than myotonic dystrophy and the disease is confined to the muscles. Serum CPK concentration may be normal or mildly increased, histological changes are slight and occasional central muscle nuclei and occasional muscle fibre atrophy may be seen.

Much experimental work has been done on the pathophysiology and genetics of these myotonic diseases (Appel and Roses, 1976). Although myotonic dystrophy and myotonia congenita are quite distinct syndromes pathologically and genetically, in both the primary disorder appears to be in the muscle membranes of either the surface or the internal sarcotubular system.

Genetic Myopathies Associated With Specific Muscle Fibre Abnormalities

Histochemical staining methods and electron microscopy have revealed in recent years specific abnormalities of muscle fibres in some cases of muscle disease which, despite arising in childhood, tend to progress slowly. Although these myopathies are uncommon, it is important that they should be recognized, as the prognosis in such cases is not so bleak as for those with Duchenne dystrophy.

These diseases are reviewed more fully elsewhere (Dubowitz and Brooke, 1973; Harriman, 1976; Gardner-Medwin, 1977), but can be summarized:

Central core myopathy. Inheritance is usually autosomal dominant, but sporadic cases occur. The central region of type I fibres is devoid of mitochondria. These cases are a potential hazard for malignant hyperpyrexia with general anaesthesia.

Nemaline myopathy. Inheritance is autosomal dominant and sporadic cases also arise. The thin needle-like rods stain blue with PTAH, red with Gomori's trichrome method, and are seen within muscle fibres often in the subsarcolemmal region; at electron microscopy they can be shown to consist of Z-line material.

Centro-nuclear or myotubular myopathy is characterized by central nuclei in muscle fibres, which on longitudinal section are seen to be arranged in long rows. Clinically, such cases are unusual myopathies as the face and extraocular muscles have been involved in most reported cases.

Mitochondrial myopathy. A number of patients complaining of weakness or pain on exercise have been found to have little abnormality on conventional histology, but oxidative enzyme stains may show mitochondrial abnormalities and, on electron microscopy, abnormally numerous mitochondria may be seen ("pleoconial myopathy"), or the mitochondria may be large ("megaconial myopathy") and amorphous or crystalline figures may be found. The mitochondrial abnormalities may be associated with fatty droplets (triglycerides) which can be seen by the light microscope; carnitine deficiency has been found in some cases.

Toxic Myopathy

An excellent review of drug-induced myopathies in man is given by Lane and Mastaglia (1978).

Steroid myopathy. The proximal muscles, particularly the quadriceps, are symmetrically involved. Severe weakness is uncommon, but weakness developing in a long course of treatment of a collagen disorder with the fluorinated steroids triamcinalone, betamethasone and dexamethasone may make a differential diagnosis between steroid myopathy, chronic polymyositis or limb girdle dystrophy difficult. In steroid myopathy serum CPK concentration is not increased. There is atrophy of type II muscle fibres, but no fibre necrosis, no phagocytosis or cellular infiltration and no extensive connective tissue or collagen infiltration.

Bupivacaine (Marcaine) myopathy. This long-acting local anaesthetic agent, when given subcutaneously or i.m. to experimental animals, produces a very rapid destruction of type I and II muscle fibres near the injection site, the changes being seen within 15 min. Regeneration of affected muscle occurs within a few days and is nearly complete by 2 weeks. Type I fibres tend to be most severely affected and sequential injections show that only mature skeletal muscle is damaged. The rapidity of myoblast to myotube to mature muscle fibre regeneration suggests that the connective tissue and muscle blood supply are relatively unaffected by the drug (Benoit and Bett, 1970).

Epsilon aminocaproic acid (EACA) (Epsicapron) myopathy. The myopathy associated with this drug may not be apparent till 5 or 6 weeks after starting treatment (Bennett, 1972; Lane et al., 1979). Serum CPK concentration may be moderately increased and an acute or subacute proximal or generalized muscle weakness develops which may be painful. Muscle biopsy shows necrosis with regeneration.

Malignant Hyperthermia (Hyperpyrexia)

The syndrome of malignant hyperthermia (MH) was first recognized in 1960. Denborough (1977) recounts how, in 1960, a 21-year-old male engineering student was brought to casualty at the Royal Melbourne Hospital, Australia, with a compound fracture of his right leg. His main concern, however, was that 10 of his close relatives had died after ether anaesthesia. Therefore halothane was used and anaesthesia was begun cautiously. After 10 min it was noted that the patient was very hot and acutely ill. Anaesthesia was stopped immediately, the patient was packed in ice, and he survived.

MH most commonly arises as an autosomal dominant trait with variable penetrance and expressivity. The frequency is 1 in 15 000 children and 1 in 50 000 adults. Mortality is still up to 70%. Halothane and suxamethonium are the agents most frequently implicated. Symptoms may arise soon after the start of anaesthesia or after some hours; often, a failure of the jaw muscles to relax for intubation after a dose of suxamethonium has been an early sign of MH. An increase in temperature and rigidity of muscles then develop, with cyanosis and acidosis. Later, myoglobinuria and cardiac irregularities may occur and disseminated intravascular coagulation is an ominous sign. Some cases do not develop muscle rigidity; this may depend on the anaesthetic drugs used. Kalow and Britt (1973) found rigidity more frequently in cases where a combination of atropine or hyoscine and suxamethonium had been used. In 20% of cases, patients have had a previous uneventful anaesthetic, although the same anaesthetic agent had been used.

Identification of cases at risk is difficult; a careful family history is most important; in some cases the serum CPK concentration is increased, but not in all. However, in some families susceptible members can be identified by this test. The only safe diagnostic procedure is to remove a small strip of muscle under local or spinal anaesthesia. This muscle is placed in a bath of Ringer's solution at 37 °C and exposed to halothane and suxamethonium when, if the patient is susceptible to MH, contracture of the test muscle occurs (Ellis et al., 1972).

Histologically, susceptible muscle may show only non-specific changes such as central nuclei and small angular fibres, but a more specific change, central core disease, has been reported in a number of cases. Eng and others (1978) report a case of MH and central core disease in a child, with an excellent recent review of MH. They doubt that myotonia congenita or myotonic atrophy have been associated with MH and MH has not been reported in Duchenne, Becker, limb girdle or facio–scapulo–humeral dystrophy nor in dermato-polymyositis syndromes. Thus the predisposing mild myopathy is often symptomless until there is exposure to a sensitizing anaesthetic agent. Indeed, some cases of MH have arisen in prominent sportsmen. Denborough (1977) describes a second type of predisposing myopathy in young boys of normal intelligence but short stature, undescended testes and skeletal abnormalities. The inheritance of this type is not clearly defined, although it is possibly recessive.

Recently, MH arose in a previously healthy 22-year-old man. A few weeks before he had had uneventful anaesthesia with suxamethonium and halothane; he was anaesthetized with the same agents for an orthopaedic procedure, but towards the end of the operation (approximately 1.5 h after induction) an increase in muscle tone was noted, associated with an increase in temperature. MH was immediately recognized but, despite intensive therapy, the patient died in renal failure the next day. At post-mortem there was marked plugging of the glomeruli with red blood cells and many tubules were filled with amorphous material interpreted as myoglobin. Some specimens of skeletal muscle showed little abnormality, but in other areas muscle striations were grossly distorted and there was extensive necrosis of muscle fibres associated with contraction bands, seen well in longitudinal section (fig. 12).

In the mid 1960s in-bred Landrace pigs were found to develop similar MH when exposed to halothane and as a result of studies on these animals and

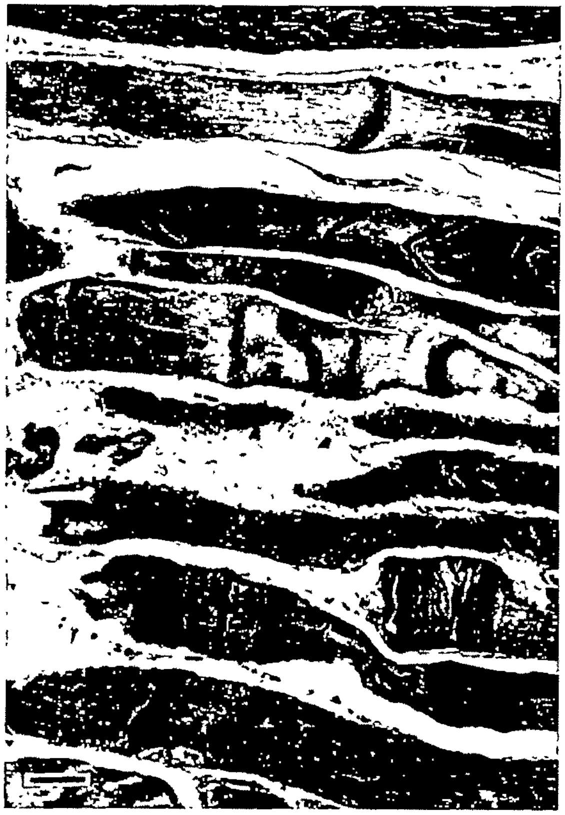


FIG. 12. Malignant hyperpyrexia, to show loss of muscle fibre striations, necrosis and presence of contraction bands. PTAH. Bar = 50 μm.

human cases it has been shown that MH is the result of excess calcium ions in the myoplasm. This is confirmed by the finding that removal of calcium ions from the test bath when susceptible muscle is exposed to halothane stops a contracture, whereas the contracture takes place when calcium is replaced. The excess of calcium may be caused by either rapid excessive release of calcium ions by the sarcoplasmic reticulum (SR) into the muscle cell or a failure to take up calcium ions by the SR. This leads to a metabolic hyperpyrexia and muscle rigidity.

The precise nature and site of the lesion are not yet clearly defined. Most workers think that certain anaesthetic agents damage a susceptible plasmalemmal membrane, upsetting the excitation–contraction coupling mechanism. Others have favoured a primary mitochondrial defect.

Malaisse and Malaisse-Lagae (1970) showed that insulin release from the beta cells of the pancreas was regulated by the calcium concentration in these cells. Later, Malaisse (1973) drew an analogy between the role of calcium in insulin release and its role in excitation–contraction in muscle. As a result of this work Denborough and colleagues (1974) studied glucose-stimulated insulin secretion in patients with the myopathy predisposing to MH. They found plasma insulin concentrations increased in these patients and suggested that the membrane abnormality in the muscle in MH may also be present in the beta cells of the pancreas.

Britt and others (1978) considered whether the muscle SR disorder present in pigs susceptible to MH when exposed to halothane was also present in the endoplasmic reticulum of the liver and might therefore contribute to the temperature increase. They perfused isolated pig livers with halothane, but did not find any significant increase in temperature.

As an excess of calcium ions in the myoplasm is the cause of MH, specific drug treatment aimed at decreasing this calcium concentration has been tried. Procaine or procainamide may be given i.v. to help to decrease calcium concentrations and stabilize the plasmalemma. Dantrolene sodium (Dantrium) is another very promising drug for reducing calcium concentrations and stabilizing the muscle membrane, but at present it can be given only orally. Hydrocortisone and dexamethasone are also used.

When a patient is known to be susceptible to MH, by family history or previous experience, local, regional or spinal anaesthesia should be used, or thiopentone, nitrous oxide and tubocurarine may be given.

Metabolic Myopathy

The main muscle fuels are glucose, glycogen and fatty acids, and by the enzymic breakdown of these substances and their final oxidation, adenine triphosphate (ATP) is formed. ATP is then used by the contractile proteins of the muscle to provide the energy for the mechanical work of contraction and relaxation. The same fuel sources and enzyme system which use ATP as the immediate source of chemical energy are found in many other systems in the body. Thus, many of these genetic enzyme defects affect other body functions as well as that of voluntary muscle.

Glycogenoses

Glycogen is metabolized in the Embden–Meyerhof cycle to pyruvate, and this may then be further metabolized without oxygen to lactic acid or, in the presence of oxygen, to carbon dioxide and water.

The aerobic metabolism produces 19 times more energy in the form of ATP than the anaerobic pathway. Disturbance of the enzyme systems in the Embden–Meyerhof cycle has been given a numerical classification, although many of these associated diseases still have eponymous labels. For a fuller account see Dubowitz and Brooke (1973) and Gardner-Medwin (1977).

Type 2 glycogenosis (Pompe's disease) is a result of acid maltase deficiency and usually presents as a floppy baby. There are deposits of glycogen in voluntary muscle, heart muscle and neurones; few cases survive to 18 months. Electron microscopy shows the glycogen to be distributed diffusely and in large granules in lysozymes. *The juvenile form* is somewhat milder, and starts later. The disease tends to progress intermittently simulating dystrophy; the heart may be involved and few cases survive 30 years. Cases of infantile type and juvenile type are probably genetically different as they have not been reported in the same family. Recently, type 2 glycogenosis has been reported in a Shorthorn herd of cattle in Western Australia.

Type 5 glycogenosis (McArdle's disease) is the result of absence of the enzyme myophosphorylase. Liver phosphorylase is present, so that only striated muscle is affected; heart and smooth muscle are normal and pregnancy and labour in such cases have proceeded normally (Cochrane and Alderman, 1973). The absence of myophosphorylase means that glycogen in muscle cannot be metabolized and collects in blebs under the sarcolemma, and no increase in lactic acid occurs in the serum after ischaemic exercise. Patients complain of cramps and pain in exercised muscles; such patients often describe the development of a "second wind" if they persist with exercise and this is thought to be a result of the utilization of free fatty acids as an alternative fuel source. This disorder is easily recognized by histochemical staining of cryostat sections of muscle for myophosphorylase, which shows complete absence of the enzyme.

Type 7 glycogenosis is caused by phosphofructokinase deficiency. Symptoms in the few cases described have been very similar to those of McArdle's disease. A histochemical test has been described for the diagnosis of this condition (Bonilla and Schotland, 1970).

Lipid myopathy

Fatty acids may be used as a fuel source, but carnitine is necessary with coenzyme A for them to enter the mitochondria for oxidation in the citric acid cycle, and carnitine palmityl transferase (c.p.t.) is necessary to link long chain fatty acids to carnitine. *Deficiency of c.p.t.* leads to cramping pains in the muscles and to myoglobinuria after exercise. The symptoms come in attacks which can be reduced if an alternative carbohydrate fuel source is given before exercise. The serum c.p.k. concentration is increased in attacks only. Muscle biopsy may be normal, but may show lipid-containing vacuoles in type I fibres.

Cases of *muscle carnitine deficiency* have been described in infancy, childhood and adult life. Some have resembled muscular dystrophy, with scapular winging and Gower's sign, and neck weakness has been noted in some. Episodes of vomiting and acidosis occurred before the myopathy in a patient whose serum, liver and muscle carnitine were decreased (Karpati et al., 1975). Biopsy shows small lipid vacuoles, mainly in type I muscle fibres. Muscle carnitine concentrations are small, but estimation of muscle carnitine is available at only a few laboratories.

REFERENCES

Adornato, B. T., Kageu, L. J., and King Engel, W. (1978). Myoglobinuria in Duchenne muscular dystrophy patients and carriers; a new adjunct to carrier detection. *Lancet*, **2**, 499.

Appel, S. H., and Roses, A. D. (1976). Membranes and myotonia; in *Pathogenesis of Human Muscular Dystrophies* (ed. L. P. Rowland), p. 747. Amsterdam, Oxford: Excerpta Medica.

Becker, P. E. (1971). Genetic approaches to the nosology of muscle diseases: myotonias and similar diseases. *Birth Defects*, **7**, 52.

Bennett, J. R. (1972). Myopathy from E-aminocaproic acid; a second case. *Postgrad. Med. J.*, **48**, 440.

Benoit, P. W., and Bett, W. D. (1970). Destruction and regeneration of skeletal muscle after treatment with a local anaesthetic bupivacaine (Marcaine). *J. Anat.*, **107**, 547.

Bonilla, E., and Schotland, D. L. (1970). Histochemical diagnosis of muscle phosphofructokinase deficiency. *Arch. Neurol.*, **22**, 8.

Bradley, W. G., Jones, M. Z., and Fawcett, P. R. W. (1978). Becker-type muscular dystrophy. *Musc. Nerve*, **1**, 111.

Britt, B. A., Shanding, B., Endrenyi, L., and Kent, G. M. (1978). Perfusion of malignant hyperthermia susceptible and normal isolated pig livers with halothane. *Can. Anaesth. Soc. J.*, **25**, 373.

Cochrane, P., and Alderman, B. (1973). Normal pregnancy and successful delivery in myophosphorylase deficiency (McArdle's disease). *J. Neurol., Neurosurg. Psychiatr.*, **36**, 225.

Denborough, M. A. (1977). Malignant hyperpyrexia. *Med. J. Aust.*, **2**, 757.

—— Warne, G. L., Moulds, R. F. W., Tse, P., and Martin, F. I. R. (1974). Insulin secretion in malignant hyperpyrexia. *Br. Med. J.*, **2**, 493.

Dubowitz, V., and Brooke, M. H. (1973). *Muscle Biopsy, a Modern Approach*. London, Philadelphia, Toronto: W. B. Saunders.

Ellis, F. R., Keaney, N. P., Harriman, D. G. F., Sumner, D. W., Kyel-Mensah, K.,Tyrrell, J. H., Hargreaves J. B., Parikh, R. K., and Mulrooney, P. L. (1972). Screening for malignant hyperpyrexia. *Lancet*, **2**, 559.

Eng, G. D., Epstein, B. S., Engel, W. K., McKay, D. W., and McKay, R. (1978). Malignant hyperthermia and central core disease in a child with congenital dislocating hips. *Arch. Neurol.*, **35**, 189.

Engel, W. K. (1961). Muscle target fibres, a newly recognised sign of denervation. *Nature* (*Lond.*), **191**, 389.

—— (1974). The vascular hypothesis: in *Recent Advances in Myology* (eds W. G. Bradley, D. Gardner-Medwin and J. B. Walton), p. 166. Amsterdam: Excerpta Medica. New York: American Elsevier Publishing Co. Inc.

Gardner-Medwin, D. (1977). Children with genetic muscular disorders. *Br. J. Hosp. Med.*, **17**, 314.

Harriman, D. G. F. (1961). Histology of the motor endplate (motor-point muscle biopsy); in *Electrodiagnosis and Electromyography*, 2nd edn (ed. S. Licht). New Haven, Connecticut: Licht.

—— (1976). Muscle; in *Greenfield's Neuropathology*, 3rd edn (eds W. Blackwood and J. A. N. Corsellis). London: Edward Arnold.

Kalow, W., and Britt, B. A. (1973). Drugs causing rigidity in malignant hyperthermia. *Lancet*, **2**, 390.

Karpati, G., Carpenter, S., Engel, A. G., Walters, G., Allen, J., Rothman, S., Klussen, G., and Mamer, O. A. (1975). The syndrome of systemic carnitine deficiency. *Neurology*, **25**, 16.

Kugelberg, I., and Welander, M. (1956). Heredo-familial juvenile muscular atrophy simulating muscular dystrophy. *Arch. Neurol. Psychiatr.*, **75**, 500.

Kuhn, E., Fiehn, W., Sieler, D., and Schroder, J. M. (1979). The autosomal recessive (Becker) form of myotonia congenita. *Musc. Nerve*, **2**, 109.

Lane, R. J. M., McLelland, N. J., Martin, A. M., and Mastaglia, F. L. (1979). Epsilon aminocaproic acid (EACA) myopathy. *Postgrad. Med. J.*, **55**, 282.

—— Mastaglia, E. L. (1978). Drug-induced myopathies in man. *Lancet*, **2**, 562.

Lindstrom, J. M., Einarson, B. L., Lennon, V. A., and Seybold, M. E. (1976). Pathological mechanisms in experimental autoimmune myasthenia gravis. I. *J. Exp. Med.*, **144**, 276.

McComas, A. J., Brandstates, M. E., Upton, A. R. M., Delbeke, J., de Faria, C., and Toyonaga, K. (1976). Sick motor neurones and dystrophy: a reappraisal; in *Pathogenesis of Human Muscular Dystrophies* (ed. L. P. Rowland), p. 180. Amsterdam, Oxford: Excerpta Medica.

Malaisse, W. J. (1973). Insulin secretion: multifactorial regulation for a single process of release. *Diabetologia*, **9**, 167.

—— Malaisse-Lagae, F. (1970). A possible role for calcium in the stimulus–secretion coupling for glucose-induced insulin secretion. *Acta Diabetol.*, Suppl. 1, 264.

Simpson, J. A. (1978). Myasthenia gravis: A personal view of pathogenesis and mechanism, Part 2. *Musc. Nerve*, **1**, 151.

Sunderland, S. (1968). *Nerves and Nerve Injuries*. Edinburgh and London: Livingstone.

De Vere, R., and Bradley, W. G. (1975). Polymyositis: its presentation, morbidity and mortality. *Brain*, **98**, 637.

Walker, M. B. (1934). Treatment of myasthenia gravis with physostigmine. *Lancet*, **1**, 1200.

Walton, J. N., and Adams, R. D. (1958). *Polymyositis*. Edinburgh: Livingstone.

—— Gardner-Medwin, D. (1974). Progressive muscular dystrophy and the myotonic disorders; in *Disorders of Voluntary Muscles*, 3rd edn (ed. J. N. Walton), Ch. 15, p. 576. Edinburgh, London: Churchill Livingstone.

Br. J. Anaesth. (1980), **52**, 153

INHERITED MUSCLE DISEASE

F. R. Ellis

The inherited diseases of muscle form a reasonably well-circumscribed group of conditions which carry an increased risk with anaesthesia as a result of both the primary muscle involvement and secondary effects, such as skeletal deformities and heart muscle disease. These diseases can be considered under four separate headings: the muscular dystrophies, the myotonias, glycogen storage diseases and the myopathies.

THE MUSCULAR DYSTROPHIES

A logical classification of the muscular dystrophies suggested by Emery and Walton (1967) is based on the mode of inheritance:

X-linked
- (a) severe (Duchenne),
- (b) mild (Becker).

Autosomal recessive
- (a) severe,
- (b) mild limb girdle (i) with facial involvement, (ii) without facial involvement.

Autosomal dominant
- (a) facio-scapulo-humeral,
- (b) distal,
- (c) ocular,
- (d) oculopharyngeal.

Severe muscular dystrophy

Although Duchenne in his original report included two girls, the X-linked recessive type of severe muscular dystrophy is named after him. Apart from the sex difference, the autosomal and the X-linked varieties of severe muscular dystrophy are similar in presentation and outcome. The disease presents in the early years of childhood in the muscles of the pelvic girdle and thighs, and the consequent weakness results in an inability to extend the trunk or the pelvis. Affected children characteristically use their arms to "climb" up their own legs when rising from the floor; this is known as Gower's sign. The disease progresses unremittingly to involve the shoulder girdle, causing winging of the scapulae, and the calves which are often found to be prominent as a result of fatty replacement of muscle tissue—the so-called pseudohypertrophy of the infant Hercules.

In the final stages the patient becomes inactive as a result of generalized muscle weakness and becomes a wheelchair invalid before death from restrictive respiratory failure, aspiration pneumonitis or from heart involvement. The age of death varies from 10 to 20 yr.

Quite early in the disease most patients develop an obstructive cardiomyopathy which can be detected on the e.c.g. and by right heart enlargement on chest x-ray. The characteristics of the e.c.g. include a large R wave in lead V1 and deep Q waves in V4–6. Inversion of the T waves in the V leads is common and there may be widening of the QRS complex with shortening of the PR interval. The standard leads often show R axis deviation. The right ventricular outflow obstruction predisposes to heart failure, a feature which can easily be overlooked because of the patient's inanition. A demonstration of the covert heart failure is a sustained increase of central venous pressure after an acute i.v. fluid load.

The diagnosis of severe muscular dystrophy can be confirmed by a greatly increased resting c.p.k. which correlates well with the progressive breakdown of muscle. C.p.k. and its isoenzymes have been used to detect the carrier state in females in families with the X-linked type.

Anaesthetic considerations

Rapid and permanent deterioration can occur with bed rest and with febrile illness, making early ambulation imperative. In the later stages of the disease respiratory weakness, which may not be recognized initially because of inactivity before operation, may result in a restrictive respiratory failure. The consequences of the weakness of the respiratory muscles and the associated weak cough predispose to sputum retention which requires active intervention to avoid the inevitable downward trend.

F. Richard Ellis, ph.d., m.b., ch.b., f.f.a.r.c.s., University Department of Anaesthesia, St James's University Hospital, Beckett Street, Leeds, LS9 7TF.

0007-0912/80/020153-12 $01.00

© Macmillan Journals Ltd 1980

A sudden tachycardia may develop during surgery, which heralds failure of the heart muscle.

Difficulty in swallowing may lead to aspiration pneumonitis in the period after operation.

In a proportion of children hyperpyrexia after operation is found, but this does not develop into malignant hyperpyrexia and is amenable to simple measures, such as surface cooling.

Hyperkalaemia may result from the rapid breakdown of muscle, hence suxamethonium and other depolarizing neuromuscular blocking drugs are inadvisable.

Other muscular dystrophies

There are several forms of muscular dystrophy which run a chronic course and do not significantly endanger or shorten life. The clinical manifestations are variable and it is often difficult to give a precise diagnosis because of overlap between them. For anaesthetists the naming of many of these conditions is largely academic as most do not involve the muscles of respiration or swallowing, and heart disease is rarely a feature.

Mild limb girdle dystrophy is an autosomal recessive condition, which affects the proximal muscles of the shoulder girdle and presents in early adult life. In the past there has been some confusion between this condition, chronic spinal muscular atrophy and polymyositis. Some patients have facial involvement and this is thought to be genetically determined.

Becker's muscular dystrophy is similar to Duchenne dystrophy, but milder. It may be confused with limb girdle dystrophy although hypertrophy of calf muscles can be obvious. Patients usually survive into middle life and there is frequently cardiac involvement similar to Duchenne dystrophy.

Dominant fascio–scapulo–humeral dystrophy has an onset in adolescence and the first symptoms are facial and shoulder muscle weakness. Later, muscles of the hips and legs are involved.

Distal muscular dystrophy is a late onset disease with presenting features associated with atrophy of the small muscles of the hands and feet. The muscles of the lower arms and legs become involved eventually.

Ocular muscular dystrophy presents with bilateral ptosis and weakness of the orbicularis muscle in middle-aged subjects. The inheritance is dominant. Sporadic cases may be confused with myasthenia gravis which also often presents with similar eye symptoms. In one form of the disease the pharyngeal muscles are involved, causing dysphagia.

Anaesthetic considerations for these conditions depend on the severity of the muscle weakness and on pharyngeal and cardiac involvement.

THE MYOTONIAS

Dystrophia myotonica

This is the most serious of the myotonic dystrophies and is inherited as an autosomal dominant characteristic. The onset is in early adult life and the disease is slowly progressive, terminating in death in middle age. It is characterized by mild myotonia, especially in cold weather and with a progressive muscular atrophy affecting initially the muscles of the face, neck, pharynx and distal limbs. The myotonia is not as severe as that seen in myotonia congenita and is not greatly incapacitating, whereas the atrophy is slowly progressive and causes severe muscle weakness in the terminal stages of the disease. The atrophy of facial muscles gives the patient a typical "myopathic" facies with ptosis, and the atrophy of the sternocleidomastoid muscle is responsible for the so-called "swan-neck" appearance.

Dystrophia myotonica involves several systems and the typical appearance of the patient is caused by the facial muscle atrophy, frontal baldness and cataracts. Testicular atrophy results in infertility. These signs are so characteristic that the diagnosis is usually not in doubt.

One of the major problems for patients with this condition is the associated heart disease. In the later stages conduction defects are commonly found and patients often die of heart failure. The electrocardiogram shows a prolonged PR interval and this may be associated with heart block. Sometimes the P wave is reduced in amplitude and there is ST elevation. Cardiac arrhythmias are common and include flutter, bradycardia and extrasystoles which are usually of ventricular origin.

The respiratory reserve is reduced, and in the more severely affected there may be a restrictive respiratory failure as a result of involvement of the respiratory muscles including the diaphragm. Respiration may be further compromised by aspiration of gastric contents, which itself may be a consequence of an abnormal swallowing mechanism resulting from involvement of the pharyngeal muscles in the disease process.

It has been suggested that patients with dystrophia myotonica have a central nervous system component and an abnormal degree of somnolence has been found.

Dystrophia myotonica can be recognized in young children and neonates, particularly if one parent is known to have the disease. In infants it may be detected as a floppy baby with delay in milestones or localized weakness with secondary skeletal abnormalities such as scoliosis. The typical myopathic facies may also be an early sign. Mental subnormality is not infrequent. Diagnosis of dystrophia myotonica can be greatly facilitated by demonstrating the spontaneous high amplitude potentials on the e.m.g. The gradual reduction in these bursts of activity produces the so-called "dive bomber" sounds when the e.m.g. is played through an audio system.

The generalized nature of the disease is evident by the lowering of plasma IgG immunoproteins which occurs as a consequence of increased catabolism.

Anaesthetic considerations

An acute and generalized myotonia has been observed with depolarizing neuromuscular blocking drugs (Paterson, 1962). All depolarizing agents and anticholinesterases should be avoided as all these drugs have been shown invariably to increase muscle tone (Orndahl and Stenberg, 1962).

Respiratory failure is caused by respiratory muscle weakness with decreases in vital capacity and maximum ventilatory volume. Oropharyngeal involvement is commonly seen and the embarrassed swallowing mechanism leads to aspiration and pneumonia.

Heart disease leads to major problems during anaesthesia. Heart block with Stokes–Adams attacks and ventricular extrasystoles with coupling can be observed frequently. Heart failure is common.

Most anaesthetic and relaxant drugs have been stated to be dangerous in patients with dystrophia myotonica. Opiates and other central respiratory depressants seem to have an exaggerated effect and this may be related to the somnolence exhibited by some patients. Body temperature should be maintained to avoid shivering after operation, which can induce generalized myotonia which itself is accentuated in cold muscles.

Myotonia congenita

Myotonia congenita was first described in 1876 by Dr Thomsen, who recognized this disease in himself and other members of his family. The distribution of the disease within his family enabled him to suggest a dominant inheritance. It has been estimated that the frequency of the dominant form of myotonia congenita is 5×10^{-6} being one-tenth of the frequency of dystrophia myotonica.

In 1948 Thomasen in Denmark recognized an autosomal recessive form of the disease which affected two siblings of unaffected parents. Becker, in extensive surveys in Germany in 1961 and 1966, found the recessive form to be commoner than the dominant and to be more severe in its clinical manifestations. He found consanguinity was present in 10% of parents of 30 of his patients in which more than one sibling was affected, and was present in eight of 69 families he investigated, that is 12%.

The clinical manifestations, which are often present at birth, are related to a tendency to develop widespread myotonia in response to rest and cold. The myotonia causes a painless stiffness of muscles which is usually relieved by exercise. Sudden movements can induce an "intention myotonia". One characteristic feature is the marked muscular development. Infants may exhibit a "strangled" cry and have difficulty in feeding.

On microscopic examination there is increased variation in fibre diameter, internal migration of nuclei and hypertrophy in some muscle fibres.

Unfortunately, the diagnosis of myotonia congenita is difficult to make because of the features it shares with paramyotonia congenita, hyperkalaemic familial periodic paralysis and, to a much lesser extent, with dystrophia myotonica.

The e.m.g. is characterized by high frequency discharges even without symptoms and this abnormality may show an abrupt onset and termination. As this is also seen in polymyositis, muscular dystrophy, myxoedema and hyperkalaemic periodic paralysis it is not pathognomonic for myotonia congenita.

Anaesthetic considerations

Depolarizing neuromuscular blocking drugs are specifically contraindicated as they will induce myotonia. Similarly, anticholinesterases are ill-advised for the antagonism of non-depolarizing relaxants because of the risk of cholinergic overactivity.

Body temperature should be monitored and hypothermia prevented by appropriate measures. It is worth noting that the hypothermic process in patients often starts before operation in response to premedication, inadequate clothing and starvation. There has been one case report (Saidman, Harvard and Eger, 1964) of malignant hyperpyrexia in a patient with myotonia congenita. Myotonia developing in response to direct surgical activation of muscle is difficult to prevent and to treat. It is uninfluenced by non-depolarizing relaxants and cannot be prevented by spinal blockade with local anaesthetics. Quinine and procainamide have been used to control myotonia in ambulant patients and it seems to lessen the abnormalities seen on the e.m.g. It may be that dantrolene could prove to be a useful drug in uncontrolled myotonia caused by direct muscle stimulation.

Familial periodic paralysis

Hypokalaemic periodic paralysis was first described in 1882. Sporadic attacks of muscle weakness affect mainly the proximal muscles. The attacks, which usually start in the second decade of life, occur frequently at night, or during a rest period after strenuous exercise, and can be brought on by eating a heavy meal especially if it contains a high proportion of carbohydrate. Other predisposing conditions are mental stress, trauma, infections and cold. An attack may last for 1–2 days, but it may be as short as a few hours. If severe, the muscle weakness results in a flaccid quadriplegia and may even affect breathing, talking and swallowing. There may be e.c.g. changes characteristic of hypokalaemia and bradycardia, and apical systolic murmurs have been described. Occasionally the attack is so severe as to cause death from respiratory failure, aspiration pneumonia or heart failure.

This disease is inherited as an autosomal dominant characteristic which is fully penetrant in males and incompletely penetrant in females. The disease is less severe in females and eventually the attacks cease. The frequency is approximately 8×10^{-6}.

It is now known that during an attack there is a positive balance for potassium, with influx of potassium into muscle cells. Patients susceptible to this condition develop a muscle weakness when the serum potassium concentration decreases to 3 mmol, but there is a marked weakness with serum potassium concentrations between 2 and 2.5 mmol. It seems that these patients are unduly sensitive to decreases of potassium, as concentrations which would not cause muscle weakness in normal individuals cause severe weakness. During an attack there is an increased thirst and a reduction in urine output and this is followed, after the attack, by a diuresis.

Various drugs have been shown to predispose to an attack of muscle weakness including insulin and glucose, adrenaline, thyroid and parathyroid hormones, ACTH, glucocorticoids and mineralocorticoids (except aldosterone). The attacks are prevented by spironolactone, diuretics, potassium therapy and a low sodium diet.

During an attack the e.m.g. shows prolongation of action potentials which, if the attack is severe enough, leads to electrical silence.

Several recent papers have described anaesthetic experiences in patients with hypokalaemic periodic paralysis. Horton (1977) reported two patients from one family who were receiving acetazolamide at the time of anaesthesia. The first patient was given droperidol and fentanyl uneventfully on one occasion and during a second anaesthetic was given droperidol, fentanyl, thiopentone, pethidine and nitrous oxide without untoward effects. The second patient had an increased arterial pressure at induction and was anaesthetized with enflurane and nitrous oxide, which produced hypotension. The patient was then given morphine and nitrous oxide. She did not recover consciousness and died of a ruptured cerebral aneurysm. In a review of their families the author reported 21 anaesthetics in eight patients and noted that on three occasions patients who had received muscle relaxants awoke with muscular weakness.

Bashford (1977) described a patient who received thiopentone, nitrous oxide and halothane for a dilatation and curettage with no untoward effects. Three years later she was admitted to hospital during pregnancy when suffering from a prolonged attack of muscle weakness, with a serum potassium concentration of 2.2 mmol. She had a Caesarean section uneventfully with thiopentone and suxamethonium, nitrous oxide, tubocurarine and papaveretum, and antagonism of the relaxant with atropine and neostigmine. It was noted that the body temperature remained constant at 36.8 °C throughout.

Siler and Discavage (1975) described a general anaesthetic in a 44-yr-old man with hypokalaemic periodic paralysis receiving long term acetazolamide and potassium chloride who required an emergency appendicectomy. Anaesthesia was induced with sodium thiamylal and maintained with halothane, nitrous oxide and a slow infusion of suxamethonium. After operation the serum potassium concentration was 2 mmol and the patient had bilateral numbness and a weakness of his toes which progressed to complete muscle paralysis. Mechanical ventilation was required for 36 h. A second anaesthetic was performed on this patient with a paravertebral block and was uneventful. A third anaesthetic for gastric surgery was performed under spinal anaesthesia using amethocaine and a general anaesthetic involving thiopentone, suxamethonium, enflurane and nitrous oxide. After operation he was satisfactory, yet the next day the patient experienced numbness and weakness of his feet and legs. Serum potassium concentration was found to be 2.6 mmol and potassium chloride was administered, with a rapid recovery.

Mental or physical trauma may lead to an attack of paralysis. Induced hypothermia during anaesthesia can lead to postoperative muscle weakness which can also occur after muscle relaxants. Serum potassium concentration should be carefully monitored and potassium supplements given as required.

Hyperkalaemic periodic paralysis. In 1957 it was recognized that familial periodic paralysis could be caused by hyperkalaemia. The characteristics of the attacks of the muscle weakness are that they are of a shorter duration (less than 1 h) than the hypokalaemic type and that they usually occur in the day and frequently whilst the patient is resting after strenuous exercise. The onset of this condition is frequently in the first decade. The weakness usually starts in the lower back and, if severe, involves the thighs, calves, and eventually the hands and arms. In very severe attacks coughing and swallowing may also be affected and occasionally blurring of vision has been encountered. Patients find that an attack can be aborted by mild exercise, although this can lead to painful lumps developing in the calf muscles. Attacks may be brought on by cold, hunger, infection and anaesthesia.

In some families myotonia is a feature of the disease and this may be a genetically distinct variety. In these patients percussion myotonia can be elicited.

The inheritance of hyperkalaemic periodic paralysis is as an autosomal dominant characteristic and there is a high degree of penetrance in both sexes. The frequency of this condition is 2×10^{-6}.

Occasionally a proximal myopathy can develop with diminished or absent tendon reflexes. During an attack the serum potassium concentration increases to more than 5 mmol, at which concentration the patient experiences weakness. If the serum potassium increases to more than 7 mmol, severe paralysis ensues. During an attack the renal excretion of potassium increases.

The e.m.g. shows high frequency and fibrillation potentials. During an attack the e.c.g. shows evidence of hyperkalaemia and peaking of the T waves often precedes paralysis.

One way of aborting the attack is to reduce the serum potassium concentration by driving it back into the cells with insulin and glucose. Other drugs have been tried, including glucagon, noradrenaline and calcium, but with limited success. The frequency of attacks can be reduced by giving the patient a high-sodium, low-potassium and high-carbohydrate diet.

In 1969 Egan and Klein described their anaesthetic experiences in three patients with this condition. Two patients developed postoperative paralysis for several hours. A prolonged period of starvation before anaesthesia may exacerbate the condition and induce an attack of paralysis. The deleterious effects of starvation can be avoided by giving the patient carbohydrate in the form of a dextrose drip. Other infusates should be potassium-free but contain sodium as the major cation.

Normakalaemic periodic paralysis may produce attacks of weakness and paralysis which last from 1 day to several weeks. The attacks are induced by stress, exertion and cold, and as with hypokalaemic periodic paralysis they occur early in the morning. The importance of this condition is that there may be cardiac involvement and arrhythmias are common. Miller and Katz (1973) suggest the use of large doses of sodium to correct both the paralysis and the cardiac arrhythmias and wonder whether procainamide or i.v. lignocaine would be helpful in counteracting the arrhythmias, as they are known to be suppressed by the use of quinidine.

Paramyotonia congenita

This condition bears some resemblence to both hyperkalaemic periodic paralysis and myotonia congenita, there being some overlap between these three conditions. The inheritance of paramyotonia is by a single autosomal dominant gene. The characteristics of this condition are myotonia and weakness which develop in response to cold. The condition frequently develops in childhood and affects mostly those muscles exposed to cold environmental temperatures such as muscles of the face and neck. Transient dysarthria or dysphagia can occur on eating ice cream. Weakness can be generalized or it may be localized to cold muscles and may persist for several days.

One characteristic feature of this condition which differs from hyperkalaemic periodic paralysis is that the muscle weakness is not improved by exercise. It is often possible to demonstrate percussion myotonia in the tongue and in the muscles of the thenar eminence.

Anaesthetic considerations

Hypothermia or even localized cooling must be avoided otherwise myotonia and muscle weakness may develop. Muscle relaxants, especially of the depolarizing variety, should be avoided in view of the danger of producing a generalized myotonic spasm.

GLYCOGEN STORAGE DISEASES

Glycogen is a high molecular weight branched polysaccaride which is formed from glucose (fig. 1). The main stores are contained in liver and both skeletal and cardiac muscle. Glycogen storage disease results from either a deficiency of one of the enzymes responsible for the breakdown of glycogen, such as phosphorylase, phosphoglucomutase or glucose-6-phosphatase, or a deficiency of one of the enzymes responsible for the branching of glycogen, such as amylo-1,6-glucosidase (debranching enzyme) or amylo-1,4- or -1,6-transglucosidase (branching enzyme).

The symptoms and signs presenting in this group of diseases depend on the target organ. Thus, if the liver is the main site of the enzyme deficiency, hepatomegaly and liver failure will result, whereas if the heart is primarily affected cardiac enlargement and heart failure will occur.

In several of these diseases skeletal muscle is involved, producing muscle weakness, pain on exertion and sometimes myoglobinuria as a result of the breakdown of the most severely affected muscle fibres.

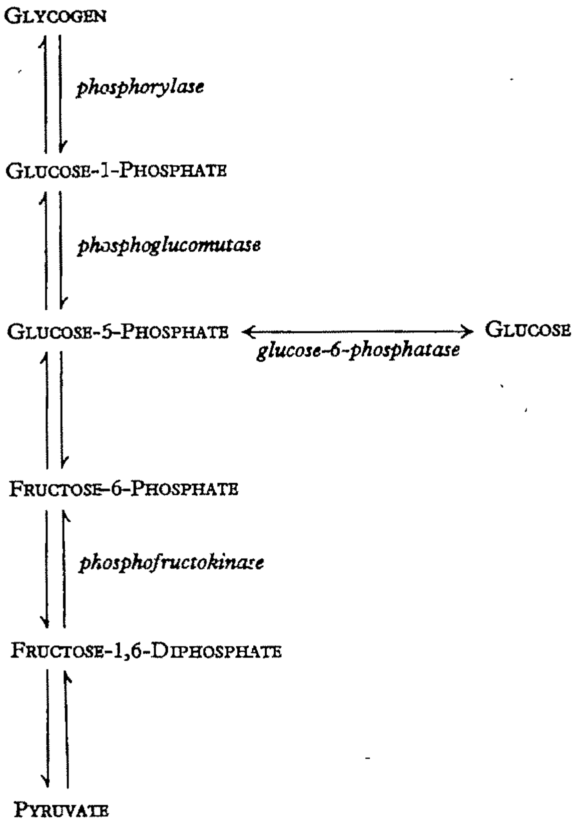


FIG. 1.

The Cori classification of the glycogen storage diseases is shown in table I; the two most commonly encountered glycogen diseases which affect skeletal muscle are dealt with at greater length. In Cori type III disease the skeletal muscle is affected, producing hypotonia and muscle weakness. In Cori type VII disease the myopathy is mild, but marked contracture of the calves have been described. In Cori type VIII (phosphofructokinase deficiency) the clinical picture is very similar to that of McArdle's disease.

There seems to be a dearth of papers describing any anaesthetic experiences in the glycogen storage

TABLE I. *Cori classification of glycogen storage diseases*

Type	Enzyme deficiency	Organs affected
Cori I (von Gierke's)	Glucose-6-phosphatase	Liver and kidneys
Cori II (Pompe's)	α-1, 4-glucosidase	Skeletal and cardiac muscle
Cori III (Cori's, Forbe's)	Amylo-1,6-glucosidase (debranching enzyme)	Liver, skeletal and cardiac muscle and blood cells
Cori IV (Andersens's)	Amylo-1,4→1,6-transglucosidase (branching enzyme)	Liver, skeletal and cardiac muscle and blood cells
Cori V (McArdle's)	Muscle phosphorylase	Muscle
Cori VI (Hers')	Liver phosphorylase	Liver and white blood cells
Cori VII (Thompson)	Phosphoglucomutase	Muscle
Cori VIII (Tarin)	Muscle phosphofructokinase	Muscle and red blood cells

diseases. The one paper devoted to this topic, by Cox (1968), describes anaesthetic experiences in type I glycogen storage (Von Gierke's) disease on many occasions.

On histology the fine aggregates of glycogen accumulate in the centre of the fibre, displacing the myofibrils to the periphery. This results in a complete disorganization of the muscle fibre and the most severely affected degenerate. The glycogen content may increase to 12% of the total weight of the muscle tissue.

In a child with Pompe's disease (Cori type II), anaesthetized for a motor-point muscle biopsy investigation, the author induced anaesthesia with nitrous oxide and a small percentage of halothane. After a couple of minutes a cardiac arrest occurred which was unresponsive to treatment. It was only after postmortem examination that it was realized that the child had Pompe's disease.

McArdle's disease

In 1951 McArdle described this condition which is characterized by muscle pain, weakness and stiffness during exercise. The onset is usually in childhood and there is diminished activity associated with muscle cramping with exercise followed by weakness. With further exercise the affected muscles may develop contractures which can only be relieved by rest. In milder degrees of exercise the muscle symptoms may regress and this has been referred to as "second wind".

McArdle's disease is a rare metabolic myopathy. The condition is inherited as an autosomal recessive and is progressive, with the development of muscle atrophy which usually occurs in the 5th decade.

Myoglobinuria can occur and it is thought that the myoglobin is released from damaged or destroyed muscle cells because of the accumulation of some metabolite as a consequence of the muscle activity exceeding the nutritional supply. The development of muscle contracture in response to severe exercise reduces blood supply to the affected muscles which become hypoxic, thus aggravating the basic metabolic defect. It has been suggested that the muscle contracture may be a result of the inability of the sarcoplasmic reticulum to reaccumulate calcium ions so that relaxation cannot be initiated.

The absence of muscle phosphorylase seems to be restricted to skeletal muscle, although one case has been described with abnormal electrocardiographic findings (Ratinov, Baker and Swaiman, 1965). In 1959 Schmit and Mahler described the chronic progressive myopathy of McArdle's disease and demonstrated that there was a glycogenolytic defect in the muscle. In the same year Schmit, Robins and Traut investigated a patient with McArdle's disease in whom they found a greatly reduced phosphorylase activity down to 0.5% of normal and also a deficiency in the enzyme which synthesizes glycogen from glucose-1,6-phosphate via the uridine diphosphate glucose pathway.

The histology of muscle usually demonstrates an increased muscle glycogen to 2–5% of the tissue weight, although in some cases it is found to be normal or even less than normal. The most specific feature is the demonstration of a greatly reduced muscle phosphorylase on neurohistochemical staining. Later in the disease muscle atrophy is found, with degeneration of some fibres.

The diagnosis of McArdle's disease can be made by measuring the venous lactate and pyruvate concentrations with ischaemic exercise. In normal individuals the lactate and pyruvate concentrations increase, whereas in McArdle's disease there is a decrease as the muscle uses the lactate and pyruvate for metabolism because of its inability to break down glycogen. Patients with McArdle's disease have an ischaemic exercise tolerance of 10–20% of normal. Another characteristic feature of this condition is the rapid decrement of evoked muscle response using electromyography with a supramaximal stimulation of a peripheral nerve. The reduction in electrical activity of these active muscles can lead to electrical silence, even in the presence of an observable muscle contracture (Dyken, Smith and Peake, 1967).

Phosphofructokinase deficiency (*Cori type VIII*) is a rare glycogen storage disease affecting the muscle and also red blood cells and produces a clinical picture very similar to that of McArdle's disease in which there is pain, stiffness and muscle weakness on exercise. Myoglobinuria has also been described following exercise. The inheritance of this condition is autosomal recessive and it has been shown that both parents of an affected child also have low phosphofructokinase activity in their muscle.

Anaesthetic considerations

Suxamethonium, by virtue of its muscle-activating properties, can result in myoglobin release causing myoglobinuria.

The use of tourniquets is contraindicated as the ischaemia may lead to muscle atrophy.

If myoglobinuria is present renal failure can be avoided by producing a forced diuresis by giving mannitol after a fluid load.

Excessive heat loss should be avoided as this would lead to shivering, especially in the period after operation, with consequent muscle damage. Also, pyrexia should be avoided as these patients do not respond well to a hypermetabolic state.

It is recommended that dextrose, fructose or lactate should be infused throughout surgery as these substances can all be used as energy sources.

INHERITED MYOPATHIES

Most of the conditions mentioned in this section are more usually known as "congenital" myopathies, although there is a clear genetic component in all of them with an autosomal pattern of inheritance.

Congenital myopathy. This condition may be either rapidly progressive or slowly progressive, both being recessively inherited. In the rapidly progressive type children are born with weakness, hypotonia and even contractures. In the slowly progressive type the child is hypotonic or floppy and may have secondary changes such as dislocation of the hips. It is sometimes difficult to distinguish a baby hypotonic as a result of muscle disease from one with subnormality.

Central core disease is a slowly progressive myopathy in which a histological defect is found. The defect is characterized by areas of rarefaction in the muscle cytoplasm and it is presumed these areas, which probably extend throughout the length of the muscle, are non-functional. One interesting feature of this condition is that it is sometimes found in association with malignant hyperpyrexia. Denborough (1973) believes the two conditions to be directly related, whereas in our experience central cores are infrequently found in malignant hyperpyrexia myopathy.

Nemaline myopathy is another histologically diagnosed condition, in which rod-shaped bundles are seen. The clinical picture may resemble Marfans syndrome with high arched palate and prognathous jaw as well as muscle weakness or hypotonia. Other skeletal abnormalities, including kyphoscoliosis, pigeon chest and pes cavus, are sometimes found. The skeletal abnormalities may reduce vital capacity, and heart failure in childhood has been described.

Myotubular myopathy is a very rare dominant condition in which muscle weakness and delay in motor milestones is associated with retention of the myotubules characteristic of fetal muscle with centrally placed nuclei. The disease progresses to produce kyphoscoliosis, ptosis and ophthalmoplegia.

Paroxysmal myoglobinuria occurs in some subjects in response to unaccustomed exercise which causes muscle breakdown with liberation of myoglobin. Repeated attacks can lead to muscle atrophy and weakness.

Anaesthetic considerations

Little is known of the way patients with the inherited myopathies respond to anaesthesia. Respiration may be embarrassed by skeletal deformity or weakness. It would seem sensible to avoid suxamethonium and similar drugs and to avoid changes of body temperature.

Malignant hyperpyrexia myopathy

Malignant hyperpyrexia myopathy (Harriman, Sumner and Ellis, 1973) is a term used to describe the abnormal pathological features found in the muscles of many patients susceptible to malignant hyperpyrexia (MHS). Unfortunately, the pathological features of MH myopathy are inconstant and great variation is found between siblings and between parents and children. The degree of morphological muscle abnormality does not in itself correlate with the severity of the MH reaction encountered and we have investigated one family in which a death occurred from MH without any abnormal muscle pathology being found in other susceptible members.

In our Investigation Unit we use two terms to describe susceptible patients. *Malignant hyperpyrexia myopathy* denotes susceptibility and a definite pathological abnormality, and in *malignant hyperpyrexia susceptibility* no pathological abnormality is found.

Pathological features

The pathological abnormalities which are commonly found in muscle include internal migration of nuclei, variation in fibre size, hypertrophy of some fibres and moth-eaten appearance of fibres stained for NADH and muscle phosphorylase. Other defects include fibre splitting, angular fibres, atrophy of one or other fibre type, degeneration and regeneration, mitochondrial swelling, central cores and targetoid fibres.

As mentioned previously, central cores which are found infrequently in our patients have been described as a consistent feature of MH myopathy.

Some of the commonly found abnormalities are seen in myotonia congenita, such as hypertrophy and internal migration of nuclei, and it is possible that there may be some overlap between these three conditions.

Clinical features and diagnostic criteria

Hyperpyrexia is a constant finding in most cases of human MH. The increase in body core temperature is progressive and often fulminating in the continued presence of the trigger drugs. Although the greatest temperature reached has an important bearing on the prognosis, it is the rate of increase which should alert to the presence of the condition. From published case reports, an increase of body temperature of 6 °C per hour is common, although the skin temperature may decrease, especially in the early stages of the disease.

Muscle contracture (rigidity, spasm) is found in most patients. It may occur after the administration of suxamethonium, although a normal response to this drug is often seen with muscle contracture developing in response to halothane or one of the other inhalation anaesthetic vapours. In a minority of patients muscle contracture either does not develop or develops at a late stage of the disease or even during recovery.

Myoglobinuria should be looked for in all suspected cases in the period immediately after operation. It may be so intense as to cause renal failure as a result of tubular obstruction. It is often possible to avoid renal failure by maintaining an increased urine output.

Hyperkalaemia is an almost invariable finding and presumably related to the muscle defect. Its presence can be detected by observing the characteristic changes on the e.c.g.

Acidosis is also an invariable finding and is caused by a rapid increase in carbon dioxide production and a marked lacticacidaemia.

Cyanosis and *tachycardia* are both frequent presenting signs, and occasionally increased oozing from wounds is seen as a result of a consumptive coagulopathy.

As anaesthetists become more aware of MH, there are increasing numbers of patients in whom a provisional diagnosis has been made before the syndrome fully develops. There are many causes of operative pyrexia, and muscle contracture with suxamethonium may indicate the presence of a myotonic muscle disease. When a provisional diagnosis of MH is made it is essential to confirm the diagnosis otherwise all members of the patient's family will have to be warned of the possible risks of anaesthesia.

Screening procedures

Patients with a history suggestive of MH and members of known MH families should be investigated to detect the presence of the MHS phenotype. The importance of the family studies lies in the fact that less than 5% of members of MH families will have inherited the abnormality and it can be argued that it is largely for the benefit of the 95% normal members that the tests should be performed.

Blood tests such as c.p.k. estimations have been proved to be too fallible for any reliance to be placed on them (Ellis et al., 1975). The only satisfactory methods are those involving muscle biopsy.

The caffeine contracture test was the first method used to identify susceptibility to MH and was developed in Toronto by Kalow and Britt (Kalow et al., 1970). All human muscle develops contracture in the presence of a sufficient concentration of caffeine, but MHS muscle is especially sensitive. At 37 °C, MHS muscle develops a significant contracture with caffeine 4 mmol, whereas normal muscle is usually unaffected. Problems may be encountered in the interpretation of results because of population overlap, and false negatives may result from poor muscle viability *in vitro*.

The halothane contracture test was first used in Leeds by Ellis and others (1971). At 37 °C MHS muscle develops a marked contracture in the presence of halothane, diethyl ether, chloroform, methoxyflurane, enflurane and trichloroethylene, whereas normal muscle is unaffected. It has been claimed by Denborough (1973) that, occasionally, normal human muscle can develop a small halothane-induced contracture and that this could lead to a false positive diagnosis. Details of the halothane contracture test are described by Ellis and others (1978). One of the major advantages claimed for this test is the lack of population overlap as a result of the idiosyncratic nature of the halothane-induced contracture in MHS muscle.

The halothane/caffeine contracture test results correlate very well with the halothane contracture test and may offer little advantage over it as a screening procedure.

Other muscle contracture tests are used, including the potassium chloride and suxamethonium contracture test (Moulds and Denborough, 1974) and the suxamethonium/caffeine contracture test (Halsall and

Ellis, 1979). The depletion of ATP in halothane-treated muscle occurs more rapidly in MHS muscle than in normal muscle and this can be used as a screening procedure (Harrison et al., 1969).

Most investigators perform a battery of tests rather than place complete reliance on one, although in our laboratory the halothane contracture test gives the most consistent results.

Treatment of MH crisis

The treatment can be considered under two headings: specific treatment and symptomatic treatment.

Specific treatment. The first drug thought to have specific properties in the treatment of MH was procaine. To be effective, a large dose was recommended and this proved to be so cardiodepressant that positive inotropic agents were required.

High-dose glucocorticoids have been successfully used on many occasions, and a direct effect of these drugs has been shown to occur by the suppression of the halothane-induced contracture by methylprednisolone *in vitro* (Ellis et al., 1974).

The recent introduction of dantrolene sodium may revolutionize the treatment of MH if the early claims for this drug can be substantiated in humans (Harrison, 1975). It can easily be demonstrated that dantrolene will reverse the halothane-induced contracture of MH muscle *in vitro*. *In vivo*, it has been shown that the increased carbon dioxide production is rapidly controlled by dantrolene (Liebenschutz, Mai and Pickerodt, 1979).

Symptomatic treatment. For a successful outcome it is usually necessary to treat the metabolic derangements aggressively and to cool the patient. Hyperkalaemia, hypoxia and acidosis all require effective and rapid reversal. After the initial treatment it may be necessary to correct hypokalaemia and to treat renal failure. Patients may remain comatose for hours or even days and, even in the latter event, full recovery is often seen.

Because of the rarity of MH, most anaesthetists should have access to a programme for its treatment. Several of these have been published and the following regime is offered only as a guide which can be adapted to particular circumstances:

(1) Terminate surgery if possible, but in any event
(2) discontinue all potent inhalation agents and depolarizing relaxants.
(3) Give 100% oxygen, preferably from an anaesthetic machine without a vaporizer.
(4) Monitor body core temperature (and limb skin if possible).
(5) Insert i.v. cannula and take venous blood sample for potassium *but* retain serum in laboratory for further investigations. Start infusion of glucose in water.
(6) Take arterial blood sample for pH, $P\text{CO}_2$ base excess and $P\text{O}_2$.
(7) Establish e.c.g.
(8) Correct electrolyte and pH inbalance on the basis of the results; repeat estimations may be needed. (Hyperkalaemia may be controlled with dextrose 50 g with insulin 20 units.)
(9) Steroid therapy: dexamethasone 1.5–2 mg kg^{-1} or methylprednisolone 7.5–10 mg kg^{-1} or hydrocortisone 30–40 mg kg^{-1}.
(10) Repeat in 15 min if no effect on rate of increase of body core temperature.
(11) Dantrolene 100 mg i.v.
(12) Give cool 5% dextrose 10–20 ml kg^{-1} h^{-1} i.v. (preferably from refrigerator or using a blood "warmer" filled with iced water). Remove all covering from patient, apply ice to groins and axillae or use fans in conjunction with tepid- or cold-water sponging using a wetting agent such as cetrimide if possible, cold water blankets, etc.
(13) Consider the following:
    (a) Procedures:
        (i) Catheterization (save first sample of urine for detection of myoglobin).
        (ii) Control of cerebral oedema and renal failure with mannitol 1 g kg^{-1}.
    (b) Drugs:
        (i) Diazepam 1 mg kg^{-1}.
        (ii) Droperidol 0.1 mg kg^{-1} as alpha-adrenaline blocker.
        (iii) Practolol 0.1 mg kg^{-1} to control arrhythmias.
        (iv) Isoprenaline 2 mg in 500 ml to increase cardiac output.

Anaesthesia for known MHS patients

General anaesthesia. As the minimum dose of halothane and other vapours which induce MH is not known, it is recommended that all vaporizers should be removed from the anaesthetic machine and that new rubber or plastic hoses, bags and connections be used.

Atropine should be avoided in premedication, but diazepam and neuroleptic drugs have proved to be reliable and safe. Thiopentone or Althesin are safe as induction agents and may be preceded by fentanyl. We use 50% nitrous oxide and if relaxation is required, pancuronium is the drug of choice, but reversal of the relaxant with anticholinesterases is not recommended, to avoid cholinergic overactivity.

Local anaesthesia. It is probably wise to avoid adrenaline in local anaesthetic solutions. Lignocaine should be avoided as it is known to activate muscle. Procaine and the other ester-linkage local anaesthetics have been recommended, although in our experience bupivacaine has proved also to be safe.

For dental extraction prilocaine has been used regularly in MHS patients and has been uneventful.

There may be a place for pretreatment of MHS patients with dantrolene although it is now possible to anaesthetize all susceptibles for any type of surgery using drugs known to be safe.

Future developments

Malignant hyperpyrexia is an eminently treatable condition. Early diagnosis is essential for a successful outcome, but this depends on monitoring body temperature during all anaesthetics in which trigger agents are being used if the time of exposure is greater than 15 min. At present, as a result of anaesthetists' greater awareness of MH, there are an increasing number of provisional diagnoses of MH made and those patients require further investigation by muscle biopsy to prove the diagnosis, followed by family studies if appropriate. As MH is a rare disorder it is hoped that, with an aggressive screening programme, the vast majority of potential cases will be screened out of the anaesthetized population.

REFERENCES

Bashford, A. C. (1977). Case report: anaesthesia in familial hypokalaemic periodic paralysis. *Anaesth. Intens. Care*, **5**, 74.

Becker, P. E. (1961). Die Heterogenie der Myotonion; in *Proc. 2nd Congr. Human Genetics*, Vol. 3. p. 1547. Amsterdam: Excerpta Media.

—— (1965). Genetik der Myopathien. *Verh. Deutsh. Ges. Inn. Med.*, **71**, 171.

Cox, J. M. (1968). Anesthesia and glycogen storage disease. *Anesthesiology*, **29**, 1221.

Denborough, M. A. (1973). Central core disease and malignant hyperpyrexia. *Br. Med. J.*, **1**, 272.

Dyken, M. L., Smith, D. M., and Peake, R. L. (1967). An electromyographic diagnostic screening test in McArdle's disease and a case report. *Neurology (Minneap.)*, **17**, 45.

Egan, T. J., and Klein, R. (1969). Hyperkalaemic periodic paralysis. *Paediatr.*, **24**, 761.

Ellis, F. R., Clarke, I. M. C., Appleyard, T. N., and Dinsdale, R. C. W. (1974). Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone. *Br. Med. J.*, **3**, 559.

—— —— Modgill, E. M., Currie, S., and Harriman, D. G. F. (1975). Evaluation of creatinine phosphokinase in screening patients for malignant hyperpyrexia. *Br. Med. J.*, **3**, 511.

—— Harriman, D. G. F., Currie, S., and Cain, P. A. (1978). Screening for malignant hyperpyrexia in susceptible patients; in *Malignant Hyperthermia* (eds J. A. Aldrete and B. A. Britt)., p. 273. New York: Grune Stratton.

—— —— Keaney, N. D., Kyei-Mensah, K., and Tyrrell, J. H. (1971). Halothane-induced muscle contracture as a cause of hyperpyrexia. *Br. J. Anaesth.*, **43**, 721.

Emery, A. E. H., and Walton, J. N. (1967). The genetics of muscular dystrophy; in *Progress in Medical Genetics V* (eds A. C. Steinberg and A. B. Bearn). London: Heinemann.

Halsall, P. J., and Ellis, F. R. (1979). A screening test for the malignant hyperpyrexia phenotype using suxamethonium-induced contracture of muscle treated with caffeine, and its inhibition by dantrolene. *Br. J. Anaesth.*, **51**, 753.

Harriman, D. G. F., Sumner, D. W., and Ellis, F. R. (1973). Malignant hyperpyrexia myopathy. *Q. J. Med.*, **42**, 639.

Harrison, G. G. (1975). Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. *Br. J. Anaesth.*, **47**, 62.

—— Saunders, S. J., Biebuyck, J. F., Hickman, R., Dent, D. M., Weaver, V., and Terblanche, J. (1969). Anaesthetic-induced malignant hyperpyrexia and a method for its premedication. *Br. J. Anaesth.*, **41**, 844.

Horton, B. (1977). Anaesthetic experiences in a family with hypokalaemic familial periodic paralysis. *Anesthesiology*, **47**, 308.

Kalow, W., Britt, B. A., Terreau, M. E., and Haist, C. (1970). Metabolic error of muscle metabolism after recovery from malignant hyperthermia. *Lancet*, **2**, 895.

Liebenschutz, F., Mai, C., and Pickerodt, V. W. A. (1979). Increased carbon dioxide production in two patients with malignant hyperpyrexia and its control by dantrolene. *Br. J. Anaesth.*, **51**, 899.

McArdle, B. (1951). Myopathy due to a defect in muscle glycogen breakdown. *Clin. Sci.*, **10**, 13.

Miller, J., and Katz, R. L. (1973). Muscle disease; in *Anaesthesia and Uncommon Diseases* (eds R. L. Katz and W. B. Kadis). Philadelphia: Saunders Co.

Moulds, R. F. W., and Denborough, M. A. (1974). Biochemical basis of malignant hyperpyrexia. *Br. Med. J.*, **2**, 241.

Orndahl, G., and Stenberg, K. (1962). Myotonic human musculature; stimulation with depolarising agents. *Acta Med. Scand.*, **172**, 389.

Paterson, I. S. (1962). Generalised myotonia following suxamethonium; case report. *Br. J. Anaesth.*, **34**, 340.

Ratinov, G., Baker, W. P., and Swaiman, K. F. (1965). McArdle's syndrome with previously unreported electrocardiographic and serum enzyme abnormalities. *Ann. Intern. Med.*, **62**, 328.

Saidman, L. J., Havard, E. S., and Eger, E. I. (1964). Hyperthermia during anaesthesia. *J.A.M.A.*, **190**, 1029.

Schmit, R., and Mahler, R. (1959). Chronic progressive myopathy with myoglobinuria: demonstration of a glycogenolytic defect in the muscle. *J. Clin. Invest.*, **38**, 1044.

—— Robins, P. W., and Traut, R. R. (1959). Glycogen synthesis in muscle lacking phosphorylase. *Proc. Natl Acad. Sci.* (Wash.), **45**, 1236.

Siler, J. N., and Discavage, W. J. (1975). Anesthetic management of hypokalemic periodic paralysis. *Anesthesiology*, **43**, 489.

Thomasen, (1948). *Myotonia*. Copenhagen: Munksgaard.

Br. J. Anaesth. (1980), **52**, 165

MALIGNANT HYPERTHERMIA—PEARLS OUT OF SWINE?

G. M. HALL, J. N. LUCKE AND D. LISTER

The safety of modern anaesthetic practice has focused the attention of anaesthetists on the very rare but potentially lethal complications of anaesthesia. One of the most interesting complications is the syndrome of malignant hyperthermia (MH) described by Denborough and Lovell in 1960. In MH the muscle of a susceptible patient reacts abnormally to suxamethonium and the potent inhalation agents with an uncontrolled increase in glycogenolysis and heat production. During the 20 years since MH was first described, clinical research has contributed little to the understanding of the syndrome. This is hardly surprising in view of the limitations imposed on investigations into MH in man. The unpredictable occurrence of the hyperthermic response during anaesthesia prevents the systematic collection of biochemical and physiological data, and the study of survivors of MH and their relatives is limited to the analysis of blood samples and muscle biopsies. Twenty years after the first description of MH the precise aetiology is unknown, the metabolic changes during the acute response have not been described adequately, and a specific therapeutic agent is not available. (An i.v. preparation of dantrolene may be on the market in the United Kingdom in 1980.) The main contribution of clinical research in MH has been in the identification of susceptible patients by the pharmacological assessment of a muscle biopsy.

The systematic study of MH requires the use of a suitable animal model. Hall and colleagues (1966) described the development of fatal hyperthermia with muscle rigidity following the administration of suxamethonium to three pigs. Since this observation extensive studies have been undertaken of MH in Landrace, Poland China and Pietrain pigs. It is often suggested that there are small differences between MH in pigs and in man, but usually a direct comparison is not possible because of the lack of accurate data for the clinical syndrome. The study of porcine MH has made important contributions to the management of patients and in particular the treatment of MH. The purpose of this paper is to describe some of the more recent developments in the porcine syndrome that are likely to be relevant to MH-susceptible patients.

Induction of porcine MH

The agents commonly used to trigger porcine MH under experimental conditions are halothane and suxamethonium, although all the potent inhalation agents can induce the syndrome. Suxamethonium alone produces fatal MH in Pietrain pigs (Lucke, Hall and Lister, 1976), and a severe but non-fatal reaction in Poland China pigs (Gronert and Theye, 1976a). The response of Poland China pigs is similar to that observed in man: the onset of MH which is not lethal providing that anaesthesia is not continued with a potent volatile agent. The administration of suxamethonium to susceptible pigs produces violent muscle fasciculations followed by a persistent increase in muscle tone and so the onset of the syndrome is clearly visible.

The use of 1% halothane to trigger MH is associated with a more insidious onset. In an animal previously anaesthetized with a barbiturate and a nitrous oxide–oxygen technique, the administration of halothane is followed by a delay of 5–10 min in Pietrain pigs (Hall, Lucke and Lister, 1976), 10–20 min in Poland China pigs (Gronert and Theye, 1976b) and 40 min in Landrace pigs (Van den Hende et al., 1976), before characteristic biochemical changes occur. These results suggest that the insistence on the use of a vapour-free anaesthetic machine for MH-susceptible patients is an unnecessary precaution.

Biochemical changes in porcine MH

The biochemical changes that occur during MH have been investigated extensively in Landrace pigs (Berman et al., 1970), in Pietrain pigs (Lucke, Hall and Lister, 1976) and in Poland China pigs (Gronert

---

G. M. HALL, M.B., B.S., PH.D., M.I.BIOL., F.F.A.R.C.S., Department of Anaesthetics, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 OHS. J. N. LUCKE, B.V.SC., M.R.C.V.S., PH.D., D.V.A., Department of Veterinary Surgery, University of Bristol, Langford, Bristol BS18 7DU. D. LISTER, B.SC., PH.D., F.I.BIOL., ARC Meat Research Institute, Langford, Bristol BS18 7DY.

Correspondence to G. M. H.

0007–0912/80/020165–07 $01.00

© Macmillan Journals Ltd 1980

and Theye, 1976a, b). There is a two- to three-fold increase in whole body oxygen consumption and an even greater increase in carbon dioxide production so that the respiratory quotient (RQ) exceeds 1.0. This is a result of the early development of a severe lactic acidosis with the buffering of the increase in hydrogen ions by the plasma bicarbonate. Thus, there is an increase in both aerobic and anaerobic muscle metabolism. Similar RQ values are found in other anaerobic states such as muscular exercise of high intensity, for example sprinting. Normal arterial oxygenation is maintained during porcine MH despite the marked desaturation found in the venous blood draining the limbs (Gronert and Theye, 1976a, b; authors' unpublished results).

Hyperglycaemia is a common but not invariable finding in porcine MH (Hall, Lucke and Lister, 1976). When present, the glucose is derived mostly from hepatic glycogenolysis with only a small contribution from gluconeogenesis (Hall et al., 1980). Lipolysis is stimulated, as shown by an increase in plasma glycerol values, but there is either a decrease or no change in plasma free fatty acid concentration (FFA). The reason for this unusual observation is obscure but may be increased re-esterification of the FFA (Hall et al., 1980).

Haemoconcentration occurs early in the hyperthermic response secondary to a shift of water into the intracellular space (Berman et al., 1970). The most important changes in plasma electrolytes are profound increases in the potassium and inorganic phosphate concentrations. Although it is often assumed that the potassium is derived from the damaged striated muscle, Hall and others (1980) have found that most of the potassium arises from the liver. The hyperphosphataemia is probably the result of the increased rate of hydrolysis of the adenine nucleotides (ATP, ADP and AMP) within the muscle. Lucke, Hall and Lister (1976) observed that the haemoconcentration was greater than the increase in plasma sodium and chloride concentrations and suggested that these ions moved intracellularly.

Hormonal changes in porcine MH

A massive increase in the plasma catecholamine concentrations during MH was described first in Pietrain pigs by Lister, Hall and Lucke (1974). This was confirmed subsequently by Gronert and Theye (1976a, b) in Poland China pigs and Van den Hende and colleagues (1976) in Landrace pigs, but the importance of this change is disputed. Gronert and Theye (1976b) considered that catecholamine increase was a secondary phenomenon arising as a result of the stress of MH, whereas Lucke, Hall and Lister (1976) have postulated that the catecholamine stimulation of muscle metabolism is an integral part of the hyperthermic response. The increase in sympathetic activity is responsible, however, for the severe tachycardia observed in MH since this is prevented by the administration of β-adrenergic blocking drugs (Lister, Hall and Lucke, 1976). The stimulation of lipolysis and hepatic glycogenolysis together with the failure of insulin secretion in the presence of a hyperglycaemia are all probably caused by the increase in catecholamine secretion (Hall et al., 1980).

Plasma glucagon concentrations show a large increase in porcine MH (Bloom, personal communication) and have a stimulatory effect on substrate mobilization similar to that of the catecholamines. Plasma cortisol concentrations only increased approximately two-fold in MH (Hall, Mashiter et al., 1976) and this may be a result of an effect of the increase in plasma noradrenaline in inhibiting ACTH secretion (Wilcox et al., 1975).

The main metabolic, electrolyte and hormonal changes in porcine MH are summarized in table I.

TABLE I. *Main metabolic, hormonal and electrolyte changes during porcine MH. The increase or decrease in plasma electrolyte values are relative to the observed haemoconcentration*

Metabolic		Hormonal	Plasma electrolytes
↑ O_2 consumption	RQ > 1.0	↑↑↑ plasma noradrenaline	↑ inorganic phosphate
↑↑ CO_2 production		↑↑ plasma adrenaline	↑ potassium
↓↓ arterial pH		↑↑ plasma glucagon	↔ magnesium
↑↑ arterial $P\text{CO}_2$		↑ plasma cortisol	↔ calcium
↑↑ blood lactate		↔ plasma insulin	↓ sodium
↑ blood pyruvate			↓ chloride
↑↑ blood glucose			
↑ plasma glycerol			
↔ or ↓ plasma FFA			

Cardiovascular changes in porcine MH

A tachycardia is an early sign of the onset of MH even when halothane is continued throughout the study. Severe arrhythmias are common, particularly after the administration of suxamethonium or in the terminal stages of the response. The cardiac output is often increased in MH despite the profound acidosis, hyperkalaemia and haemoconcentration (Gronert and Theye 1976b; Lucke, Hall and Lister, 1976) and myocardial metabolism is normal (Gronert et al., 1978). It is unlikely, therefore, that there is any abnormality of cardiac muscle in porcine MH, although in the human syndrome it has been suggested that a cardiomyopathy is present in some susceptible patients (Britt, 1974). Intense peripheral vasoconstriction is apparent by the cyanotic mottling of the skin observed in the established syndrome and contributes to the hyperthermia by reducing heat loss. The changes in arterial pressure during MH are not consistent as both hypertension (Lucke, Hall and Lister, 1976) and hypotension (Gronert and Theye, 1976b) have been reported. When the metabolic changes are extreme in the terminal stages of MH, the cardiac output and arterial pressure decrease rapidly and cardiac arrest occurs.

Heat production in porcine MH

The primary source of heat production in MH is skeletal muscle. During MH the temperature increase is detected first in muscle and Clarke and others (1973) showed that the temperature of the femoral venous blood was up to 2 °C greater than that measured in the femoral artery. Increased thermogenesis may occur in other organs such as the liver (Berman et al., 1970), but their contribution is small compared with that of skeletal muscle, which is responsible for about 45% of the body weight. The muscle temperature may increase as rapidly as 1 °C per 5 min, but it must be emphasized that the hyperthermia is just one manifestation of the increase in muscle metabolism. If the hyperthermia is controlled by cooling, then the pig still dies with severe metabolic changes although with a normal body temperature. The implications for the treatment of the syndrome are obvious.

Hall, Bendall and others (1976) attempted to determine the contributions of aerobic and anaerobic muscle metabolism to the heat production in MH. They concluded that in the initial stages of the response the thermogenesis was mostly aerobic in origin. Aerobic metabolism was responsible for only half the increase in temperature observed terminally, but the accumulation of lactate within the muscle (anaerobic metabolism) accounted for the remainder. The importance of aerobic heat production in the early stages of MH was confirmed by Gatz, Kerr and Wingard (1978).

Aetiology of porcine MH

The primary defect in MH is assumed to be an abnormality of calcium regulation, since three of the primary features of MH, increased glycogenolysis, heat production and muscle tone, can all be explained by the presence of an abnormally great calcium concentration with the cytoplasm of the muscle cell. It is noteworthy that this increase in calcium concentration is inferred and has never been measured.

The subcellular organelle(s) responsible for the defect in calcium homeostasis has not been identified. The sarcoplasmic reticulum, the mitochondria and the sarcolemma have all been implicated, but the experimental evidence is inconclusive. The most popular site for the defect, at present, is in the region of the junction of the sarcolemma and sarcoplasmic reticulum. It is likely that the abnormality responsible for MH is only an exaggeration of a normal biochemical phenomenon, for example alteration in calcium binding to a membrane, as the pigs grow and develop normally unless challenged by anaesthetic agents or a severe environmental stress. The elucidation of this problem is particularly difficult because the stimulus of taking a muscle biopsy is sufficient to stimulate glycogenolysis and prevent an accurate representation of the *in vivo* state.

Treatment of porcine MH

The treatment of porcine MH is best considered in terms of general supportive therapy and the use of specific therapeutic agents.

Gronert, Milde, and Theye (1976a) found that in fulminating MH, the discontinuation of the anaesthetic agent, hyperventilation with oxygen, surface cooling and the use of sodium bicarbonate only prolonged the course of the response and that all the pigs died eventually. These therapeutic measures are likely to be more successful if applied earlier in the response and the rapid correction of the acidosis is particularly important. In MH in man, which is usually less severe than the porcine model, the general supportive therapy outlined above may be effective without the use of other agents. Because the precise aetiology of MH is unknown it has been difficult to devise specific therapeutic agents. Procaine or procainamide, magnesium, corticosteroids and dantrolene have all been investigated.

Procaine or procainamide. Harrison (1971) described the successful treatment of MH with large doses of i.v. procaine in two out of five Landrace pigs. This result encouraged the use of procaine in the clinical syndrome in spite of the myocardial depression associated with the i.v. administration of procaine 30 mg/kg body weight. Some clinical case reports suggested that procaine was beneficial, but the specific effects of the drug could not be determined because of the multiplicity of other therapeutic agents.

Further studies using procaine or procainamide to treat porcine MH have all failed to reproduce Harrison's results. These compounds were totally ineffective in Landrace cross-bred pigs (Hall, Trim and Woolf, 1972), Pietrain pigs (Hall and Lister, 1974), Landrace pigs (Mitchell and Heffron, 1975) and Poland China pigs (Gronert, Milde and Theye, 1976b). Gronert, Milde and Theye (1976b) found that not only was procaine of no value in the acute treatment of MH, but also it was of no benefit when given prophylactically before MH was induced.

Magnesium sulphate. Hall, Lucke and Lister (1975) found that the administration of i.v. magnesium sulphate was successful in six of 15 hyperthermic pigs —a success rate identical to Harrison (1971) with procaine. The principal drawback to the use of magnesium sulphate was the inhibition of skeletal muscle and myocardial metabolism at similar very great plasma magnesium concentrations, so that the resolution of MH was often associated with a cardiac arrest! The possible benefits of magnesium sulphate in porcine MH have not been investigated by other workers and there is no report of its use in man.

Corticosteroids. Ellis and colleagues (1974) recommended the empirical use of large doses of corticosteroids such as hydrocortisone and dexamethasone for the treatment of MH in man. The only study examining the effects of steroids in porcine MH was reported by Hall, Lucke and Lister (1977b). They found that i.v. injection of methylprednisolone 30 mg/kg body weight was of no value in the treatment of the established syndrome and the course of the hyperthermic response was unaltered.

Dantrolene. In 1975 Harrison recorded the success of i.v. dantrolene, a hydantoin derivative, in the treatment of MH in Landrace pigs. Unlike procaine, this result was confirmed in Poland China pigs by Gronert, Milde and Theye (1976a) and in Pietrain pigs by Hall, Lucke and Lister (1977a). Furthermore, Gronert, Milde and Theye (1976a) observed that porcine MH could be prevented by using i.v. dantrolene before the administration of halothane and suxamethonium. Harrison (1977) extended this observation by demonstrating that oral dantrolene in the Landrace pig was also effective as prophylaxis against MH. Dantrolene is, therefore, the only consistently effective agent in the treatment of porcine MH. When a suitable i.v. dantrolene preparation is available for routine clinical use (possibly mid-1980 in the United Kingdom), then the validity of using porcine MH as a model for the treatment of the clinical syndrome will be ascertained.

The effects of the specific therapeutic agents are summarized in table II.

TABLE II. *Effectiveness of specific therapeutic agent in porcine MH*

Drug	Acute treatment	Prophylaxis
Procaine or procainamide	Ineffective	Ineffective
Magnesium sulphate	Partially effective dangerous side-effects	Not tested
Corticosteroids	Ineffective	Not tested
Dantrolene	Effective	Effective

Inheritance of porcine MH

The exact mode of inheritance of porcine MH is uncertain. Indeed, the situation is nearly as confusing as that described for MH in man. Early studies suggested that porcine MH was inherited as a single autosomal dominant gene with incomplete pentrance and variable expressivity (Woolf et al., 1970); as a single strongly modified gene, or even two dominant genes acting together (Williams et al., 1975). More recent investigations using a halothane challenge to identify susceptible pigs showed that MH was inherited as an autosomal recessive characteristic (Andresen and Jensen, 1977; Eikelenboom et al., 1978). It is possible that the pattern of inheritance differs from breed to breed and from herd to herd, but experimental breeding programmes strongly support the contention that halothane sensitivity is controlled by one major recessive gene with complete penetrance (Eikelenboom et al., 1978).

Rasmusen and Christian (1976) demonstrated a correlation between halothane susceptibility in pigs and the presence of certain blood types in the H system of red cell antigens. In addition, there is a close link between the H blood group system and the presence of phosphohexose isomerase and 6-phosphogluconate dehydrogenase (Andresen, 1971;

Andresen and Jensen, 1977). The use of enzyme markers and red cell antigens to identify susceptible animals and determine the mode of inheritance is an interesting development and may prove to be a useful and safer alternative to the halothane challenge.

Factors modifying susceptibility to porcine MH

It is wrong to assume that a pig which is susceptible to MH will always develop a fatal response when given a certain concentration of anaesthetic agent such as 1% halothane for 20 min. Many factors can modify the sensitivity of the muscle to the triggering agent and the two which have received the greatest attention are the sympathetic nervous system and the extent of previous muscle activity.

Sympathetic nervous system. Our experiments in Pietrain pigs suggest that the sympathetic nervous system has an important role in porcine MH. Perhaps the most conclusive study was the demonstration that Pietrain pigs which had undergone bilateral adrenalectomy together with pretreatment with bretylium tosylate were totally protected from halothane (Lucke et al., 1978). On the other hand, Gronert, Milde and Theye (1977) used total spinal anaesthesia to produce sympathetic blockade in Poland China pigs, but found that all the animals still developed MH on exposure to halothane. It is difficult to reconcile these totally opposing views.

There is other indirect evidence to suggest that excessive sympathetic activity in MH-susceptible pigs will stimulate muscle metabolism. These animals may respond to various adverse environmental conditions such as restraint, transport, heat, etc., with the development of a fatal hyperthermia (porcine stress syndrome). The biochemical changes observed in the porcine stress syndrome reflect a large increase in muscle glycogenolysis.

If it is accepted that catecholamines can increase the sensitivity of porcine muscle to halothane, then their mode of action is not readily apparent. The results of Lister, Hall and Lucke (1976) and Hall, Lucke and Lister (1977c) indicate that stimulation of α-adrenergic receptors is more important than β-adrenergic stimulation, and yet most of the effects of catecholamines on muscle metabolism are known to be mediated via the β-adrenoreceptors. Recent studies on tissues having both α- and β-metabolic effects showed that, whereas β-adrenergic stimulation always occurs via the adenyl cyclase–cyclic AMP system, α-stimulation is dependent on changes in the intracellular calcium concentration (Thompson and Williamson, 1976).

Mogensen, Misfeldt and Hanel (1974) suggested that, in the clinical syndrome, excitement and apprehension before operation may make an individual more susceptible to MH, and Wingard (1974) described an MH family whose members were "stress-susceptible" in a way similar to the porcine stress syndrome described above.

Muscle activity. Berman (1973) suggested that excessive muscle activity or trauma may increase the likelihood of a patient developing MH. A dramatic experimental verification of this hypothesis was provided by Van den Hende and others (1976) in Belgian Landrace pigs. They found that a short period of exercise 1 h before anaesthesia increased the susceptibility of the pigs from 42% to 100%. Conversely, Hall, Lucke and Lister (1976) observed that pretreatment with pancuronium in Pietrain pigs afforded some protection against halothane, and Lucke (1975) reported that deep pentobarbitone anaesthesia also decreased the sensitivity of the muscle.

A simple concept may explain the many different factors that influence the susceptibility of an individual animal. MH is triggered when a critical calcium concentration is reached within the muscle cell. The initial calcium concentration present when the pig is exposed to the triggering agent depends on previous exercise, drugs administered, sympathetic nervous system, etc. This is shown most readily in the "halothane challenge" in which an awake pig is restrained and forced to breathe halothane to test for MH susceptibility. If the animal is susceptible, obvious signs of MH occur within 5 min. A previously anaesthetized pig, however, takes from 10 to 40 min to develop MH, depending on the breed. Thus, the occurrence of MH in response to a known concentration of triggering agent cannot be regarded as an "all-or-none" phenomenon.

Related syndromes

Pigs susceptible to MH also have an increased likelihood of developing the porcine stress syndrome (PSS) and of producing pale, soft exudative pork (PSEP). All three syndromes are associated with an uncontrolled increase in muscle glycogenolysis. In the case of PSEP the enhanced glycogenolysis is induced by slaughter and produces meat of an inferior quality. There is a strong link between the susceptibility to MH, PSS and PSEP and the body composition of the pig. Susceptible animals are extremely muscular, with little subcutaneous fat and their overall body length is short. The reason for this association is not clear, but the differential deposition of body fat internally rather than subcutaneously suggests the occurrence of small differences in endocrine function between susceptible and non-susceptible pigs.

In conclusion, the validity of the porcine syndrome as a model for MH in man will be thoroughly examined in the next few years. Time will tell if there is any clinical wisdom to be obtained from a study of hyperthermic pigs.

ACKNOWLEDGEMENTS

G. M. Hall received generous financial support from the Muscular Dystrophy Group of Great Britain. Shirley Richens and Gabrielle Mead provided skilled secretarial assistance.

REFERENCES

Andresen, E. (1971). Linear sequence of the autosomal loci PHI, H and 6-PGD in pigs. *Anim. Blood Groups Biochem. Genet.*, **2**, 119.

—— Jensen, P. (1977). Close linkage established between the locus of halothane sensitivity and the PHI (phosphohexose isomerase) locus in pigs of the Danish Landrace breed. *Nord. Vetinaer Med.*, **29**, 502.

Berman, M. C. (1973). The role of preoperative management in development of malignant hyperthermia. *Lancet*, **2**, 743.

—— Harrison, G. G., Bull, A. B., and Kench, J. E. (1970). Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. *Nature (Lond.)*, **225**, 653.

Britt, B. A. (1974). Malignant hyperthermia: a pharmacogenetic disease of skeletal and cardiac muscle. *N. Engl. J. Med.*, **290**, 1140.

Clarke, M. G., Williams, C. H., Pfeifer, W. E., Bloxham, D. P., Holland, P. C., Taylor, C. A., and Lardy, H. A. (1973). Accelerated substrate cycling of fructose-6-phosphate in muscle of malignant hyperthermic pigs. *Nature (Lond.)*, **245**, 99.

Denborough, M. A., and Lovell, R. R. H. (1960). Anaesthetic deaths in a family. *Lancet*, **1**, 45.

Eikelenboom, G., Minkema, D., Van Eldik, P., and Sybesma, W. (1978). Inheritance of the malignant hyperthermia syndrome in Dutch Landrace swine; in *Malignant Hyperthermia* (eds J. A. Aldrete and B. A. Britt), p. 141. New York: Grune and Stratton Inc.

Ellis, F. R., Clarke, I. M. C., Appleyard, T. N., and Dinsdale, R. C. W. (1974). Malignant hyperpyrexia induced by nitrous oxide and treated with dexamethasone. *Br. Med. J.*, **3**, 559.

Gatz, E. E., Kerr, D. D., and Wingard, D. W. (1978). Earlier diagnosis of malignant hyperthermia; in *Malignant Hyperthermia* (eds J. A. Aldrete and B. A. Britt), p. 147. New York: Grune and Stratton Inc.

Gronert, G. A., Milde, J. H., and Theye, R. A. (1976a). Dantrolene in porcine malignant hyperthermia. *Anesthesiology*, **44**, 488.

Gronert, G. A., Milde, J. H., and Theye, R. A. (1976b). Porcine malignant hyperthermia induced by halothane and succinylcholine: failure of treatment with procaine or procainamide. *Anesthesiology*, **44**, 124.

—— —— —— (1977). Role of sympathetic activity in porcine malignant hyperthermia. *Anesthesiology*, **47**, 411.

—— Theye, R. A. (1976a). Suxamethonium-induced porcine malignant hyperthermia. *Br. J. Anaesth.*, **48**, 513.

—— —— (1976b). Halothane-induced porcine malignant hyperthermia. Metabolic and haemodynamic changes. *Anesthesiology*, **44**, 36.

—— —— Milde, J. H., and Tinker, J. H. (1978). Catecholamine stimulation of myocardial oxygen consumption in porcine malignant hyperthermia. *Anesthesiology*, **49**, 330.

Hall, G. M., Bendall, J. R., Lucke, J. N., and Lister, D. (1976). Porcine malignant hyperthermia. II: Heat production. *Br. J. Anaesth.*, **48**, 305.

—— Lister, D. (1974). Procaine and malignant hyperthermia. *Lancet*, **1**, 208.

—— Lucke, J. N., and Lister, D. (1975). Treatment of porcine malignant hyperthermia. A review based on experimental studies. *Anaesthesia*, **30**, 308.

—— —— —— (1976). Porcine malignant hyperthermia. IV: Neuromuscular blockade. *Br. J. Anaesth.*, **48**, 1135.

—— —— —— (1977a). Treatment of porcine malignant hyperthermia. The successful use of dantrolene in the Pietrain pig. *Anaesthesia*, **44**, 36.

—— —— —— (1977b). The failure of methylprednisolone treatment in porcine malignant hyperthermia. *Lancet*, **2**, 1359.

—— —— —— (1977c). Porcine malignant hyperthermia. V: Fatal hyperthermia in the Pietrain pig associated with infusion of α-adrenergic agonists. *Br. J. Anaesth.*, **49**, 855.

—— —— Lovell, R., and Lister, D. (1980). Porcine malignant hyperthermia. VII: Hepatic metabolism. *Br. J. Anaesth.*, **52**, 11.

—— Mashiter, K., Lucke, J. N., and Lister, D. (1976). Hormonal changes in porcine malignant hyperthermia. *Br. J. Anaesth.*, **48**, 930.

Hall, L. W., Trim, C. M., and Woolfe, N. (1972). Further studies on porcine malignant hyperthermia. *Br. Med. J.*, **2**, 145.

—— Woolf, N., Bradley, J. W. P., and Jolly, D. W. (1966). Unusual reaction to suxamethonium chloride. *Br. Med. J.*, **4**, 1305.

Harrison, G. G. (1971). Anaesthetic-induced malignant hyperpyrexia: a suggested method of treatment. *Br. Med. J.*, **3**, 454.

—— (1975). Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. *Br. J. Anaesth.*, **47**, 62.

—— (1977). The prophylaxis of malignant hyperthermia by oral dantrolene sodium in swine. *Br. J. Anaesth.*, **49**, 315.

Lister, D., Hall, G. M., and Lucke, J. N. (1974). Catecholamines in suxamethonium-induced hyperthermia in Pietrain pigs. *Br. J. Anaesth.*, **46**, 803.

—— —— —— (1976). Porcine malignant hyperthermia. III: Adrenergic blockade. *Br. J. Anaesth.*, **48**, 831.

Lucke, J. N. (1975). A study of porcine malignant hyperthermia. Ph.D. Thesis, University of Bristol.

Lucke, J. N., Denny, H. R., Hall, G. M., Lovell, R., and Lister, D. (1978). Porcine malignant hyperthermia. VI: The effects of bilateral adrenalectomy and pretreatment with bretylium on the halothane-induced response. *Br. J. Anaesth.*, **50**, 241.

—— Hall, G. M., and Lister, D. (1976). Porcine malignant hyperthermia. I: Metabolic and physiological changes. *Br. J. Anaesth.*, **48**, 297.

Mitchell, G., and Heffron, J. J. A. (1975). Procaine in porcine malignant hyperthermia. *Br. J. Anaesth.*, **47**, 667.

Mogensen, J. V., Misfeldt, B. B., and Hanel, H. K. (1974): Preoperative excitement and malignant hyperthermia. *Lancet*, **1**, 461.

Rasmusen, B. A., and Christian, L. L. (1976). H blood types in pigs as predictors of stress susceptibility. *Science*, **191**, 947.

Thompson, M. R., and Williamson, D. H. (1976). Metabolic effects of alpha- and beta-adrenergic stimulation of rat submaxillary gland *in vitro*. *Biochem. J.*, **160**, 597.

Van den Hende, A., Lister, D., Muylle, E., Ooms, L., and Oyaert, W. (1976). Malignant hyperthermia in Belgian Landrace pigs rested or exercised before exposure to halothane. *Br. J. Anaesth.*, **48**, 821.

Wilcox, C. S., Aminoff, M. J., Millar, J. G. B., Keenan, J., and Kremer, M. (1975). Circulatory levels of corticotrophin and cortisol after infusions of L-dopa, dopamine and noradrenaline in man. *Clin. Endocrinol.*, **4**, 191.

Williams, C. H., Lasley, J. F., Muhrer, M. E., and Hedrick, H. B. (1975). Relationship between fulminating hyperthermia and the porcine stress syndrome. *J. Anim. Sci.*, **41**, 261.

Wingard, D. W. (1974). Malignant hyperthermia: a human stress syndrome. *Lancet*, **2**, 1451.

Woolfe, N., Hall, L., Thorne, C., Down, M., and Walter, R. (1970). Serum creatine phosphokinase levels in pigs reacting abnormally to halogenated anaesthetics. *Br. Med. J.*, **3**, 386.

Br. J. Anaesth. (1980), **52**, 173

NEUROMUSCULAR PHARMACOLOGY

A clinical update and commentary

C. LEE AND R. L. KATZ

This review stresses those areas of neuromuscular pharmacology where recent advances of clinical interest have been made. It is meant to be a general didactic review, rather than an exhaustive coverage of the literature.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Pharmacokinetics involves studies of the serum concentrations of drugs, but not studies of the drug effects. Recently, radioimmunoassay, fluorimetric and chromatographic techniques (Horowitz and Spector, 1973; Kersten, Meijer and Agoston, 1973) have greatly facilitated the determination of the serum concentration of the neuromuscular blockers. Readers interested in the principles of pharmacokinetics are referred to Greenblatt and Koch-Weser (1975), Hug (1978) and Hull (1979) for recent reviews. Whether a three-compartment model (Gibaldi, Levy and Hayton, 1972) or a two-compartment model (McLeod, Watson and Rawlins, 1976) is more appropriate for the neuromuscular blocking drugs injected i.v. is mainly of academic interest. These compartments are central, peripheral I and peripheral II (Gibaldi, Levy and Hayton, 1972), central, specific and non-specific (Buzello and Agoston, 1978), or central and peripheral (McLeod, Watson and Rawlins, 1976). For practical purposes, a two-compartment model suffices.

The decay of the serum concentration following i.v. administration of the relaxants can be divided, for simplicity, into two phases (fig. 1). Distribution to tissues, particularly to the sites of action, which is accompanied by onset of neuromuscular block, occurs during the initial (distribution, α) phase. Increased cardiac output and tissue perfusion will reduce the time requirement of this phase. The slower second (elimination, β) phase of continued decay is the result of metabolism, excretion and uptake by non-specific "sites of inactivity". Many factors will reduce the plasma clearance of the neuromuscular blockers.

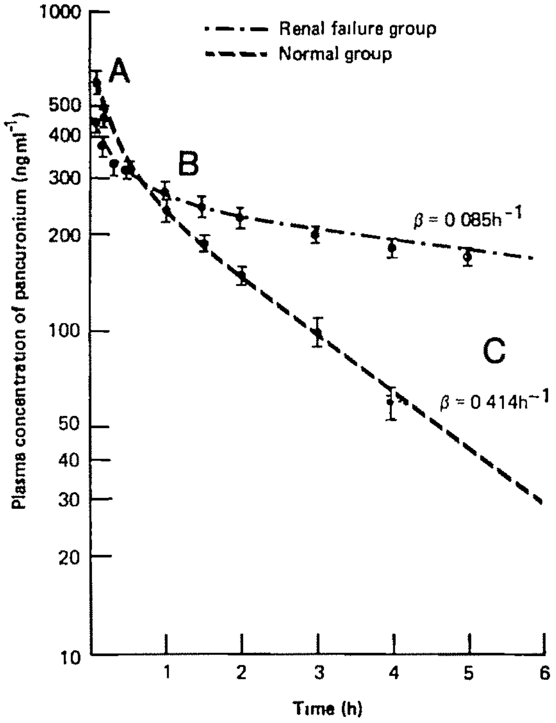


FIG. 1. Pharmacokinetics of pancuronium bromide following i.v. injection (4 mg) in man, and the effect of renal failure. From A to B: distribution (α) phase, when the plasma concentration decreases rapidly. From B to C and on: elimination (β) phase, when the concentration decreases more gradually. Chronic renal failure increases the initial distribution volume (see lower initial plasma concentration) but reduces the rate of elimination (see less steep terminal decay slope) of pancuronium. The markedly reduced elimination rate may markedly increase the duration of action of pancuronium or the duration of time when significant cumulation of effect or residual receptor occlusion may occur (modified from McLeod, Watson and Rawlins, 1976).

Besides the half-lives (distribution half-life and elimination half-life) or time constants of decay of the

---

CHINGMUH LEE, M.D.; RONALD L. KATZ, M.D.; Department of Anesthesiology, UCLA Medical Center, Los Angeles, California 90274, U.S.A.

0007-0912/80/020173-16 $01.00

© Macmillan Journals Ltd 1980

serum concentration, pharmacokinetics deals with the so-called volume of distribution and the rate of transfer of drugs among the various compartments. Because neuromuscular blocking agents are highly ionized, they have a limited volume of distribution following i.v. injection. The imaginary volume of distribution which governs the initial dose–concentration relationship ranges from 14 to 80 ml kg^{-1} and is not much larger than the blood volume.

It is important to realize that abnormal conditions may not alter the volume of distribution, the sensitivity of the neuromuscular junction and the rate of elimination in the same direction. Patients with renal failure, for example, may not require less relaxant to establish a desired block initially, but may subsequently require an abnormally prolonged time for neuromuscular transmission to recover.

Renal failure affects the pharmacokinetics of the neuromuscular blockers (fig. 1), particularly the kinetics of those blockers which depend primarily on renal excretion for elimination (McLeod, Watson and Rawlins, 1976; Buzello and Agoston, 1978). Gallamine, metocurine and decamethonium depend almost entirely on the kidneys for their elimination. Pancuronium is approximately twice as dependent on the kidneys for elimination as is tubocurarine (Miller, Agoston, van der Pol et al., 1978). From this point of view, tubocurarine may be a better choice in patients with renal failure. Besides increased duration of neuromuscular block, patients with renal failure are more prone to cumulative effect, and prolonged residual receptor occupation may deplete neuromuscular reserve for a long time (Waud and Waud, 1972).

However, with careful monitoring and appropriate adjustment of the dose schedule most neuromuscular blockers can be used safely for most surgical conditions in patients with renal failure. In general, an initial "intubation" dose and a small supplemental dose are tolerated. Even without metabolism or excretion, redistribution of the blocker away from the site of action will result in sufficient spontaneous recovery so that satisfactory reversal of the block can be achieved. If the residual serum concentration is low, and if successful reversal has once been achieved, recurrent block is unlikely. One additional safety factor is that, in the absence of renal function, alternative routes of elimination will assume an increased role. The reversal agents also last longer (Burdfield and Calvey, 1973; R. Cronnelly, personal communication). Interestingly, newly transplanted kidneys are capable of excretion of tubocurarine (Miller et al., 1977) and neostigmine (R. Cronnelly, personal communication).

Hepatic failure affects pharmacokinetics less profoundly. Most neuromuscular blockers are either independent or only partially dependent upon the liver for elimination. Parenchymal disease may reduce hepatic uptake and metabolism. Biliary obstruction may reduce excretion (Somogyi, Shanks and Triggs, 1977). Unlike most other neuromuscular blockers, pancuronium is metabolized by the liver to a significant degree. Approximately 25–45% of an injected dose of pancuronium is de-acetylated into 3-OH, 17-OH or 3,17-OH pancuronium. Of these only the main (3-OH) metabolite has significant neuromuscular blocking potency, being one-third to one-sixth (Agoston et al., 1977) or up to nearly one-half (Miller, Agoston, Booij et al., 1978) as potent as is pancuronium in man. Since the metabolites appear only in small quantities and do not have longer durations of action, they are unlikely to be the cause of prolonged paralysis (Agoston et al., 1973).

Protein binding may also be altered by renal and hepatic failures. While pancuronium is not bound to serum proteins to a significant degree, tubocurarine is (Ghoneim et al., 1973). Protein-bound relaxant molecules do not act on the cholinergic receptors. Neither are they readily excreted by glomerular filtration. In practice, the effect of abnormal protein binding is rarely ascertained.

Besides abnormal pharmacokinetics, patients may have an abnormal *sensitivity* to muscle relaxants. For clarity, it seems desirable to restrict the term *neuromuscular sensitivity* to the description of the relation between the magnitude of block and the serum concentration of the blocker. An individual may be abnormally *susceptible* to a given dose of a blocker either because the resultant serum concentration is abnormally great (pharmacokinetics) or because an abnormally profound block results from a normal concentration (sensitivity), or both.

Hypothermia affects a multitude of factors which may in turn enhance and prolong neuromuscular block. These factors include muscle perfusion, hepatic and renal perfusion, metabolism, protein binding, excretion and abnormal neuromuscular sensitivity. In terms of pharmacokinetics, Miller, Agoston, van der Pol and others (1978) and Ham and others (1978) have shown that hypothermia reduced hepatic and renal elimination of both pancuronium and tubocurarine. In terms of neuromuscular sensitivity, Miller's study revealed an increased sensitivity to pancuronium (a reduced serum concentration requirement of pancuronium for a given degree of block) under hypothermia. Strangely, Ham's study revealed an opposite effect of hypothermia on the neuromuscular sensitivity to tubocurarine.

Drug interaction

Antibiotics enhance the neuromuscular blocking effects of muscle relaxants. Since the reviews by Pittinger, Eryasa and Adamson (1970) and by Pittinger and Adamson (1972), amikacin (Hashimoto et al., 1978), tobramycin (Waterman and Smith, 1977) and clindamycin (Fogdall and Miller, 1974) have been added to the list of antibiotics causing prolonged paralysis. Observations since then have also demonstrated that pancuronium interacts with the neuromuscular blocking antibiotics as tubocurarine does. Pittinger and associates (1970, 1972) classified the neuromuscular blocking antibiotics into four groups: aminoglycosides, polypeptides, tetracyclines and miscellaneous antibiotics (e.g. lincomycin). Aminoglycosides are most numerous and include neomycin and streptomycin. The newer aminoglycosides tobramycin and amikacin are weaker neuromuscular blockers than neomycin. The polypeptide group is exemplified by polymixin B, which produces one of the most protracted types of neuromuscular block.

Besides neuromuscular block, neomycin and streptomycin may depress cardiovascular and ganglionic function. Polymixin B appears to depress all excitable tissues. It causes hypotension, bradycardia, ganglion block, postganglionic autonomic block, histamine release, nerve block and cataract formation (Wright and Collier, 1976; Lee, Ricker and Katz, 1979). It is highly lethal to the cat, even if the cat is properly ventilated (personal observation). While aminoglycoside-induced neuromuscular block is at least partially reversible by cholinesterase inhibitors and by calcium, polymixin B-induced neuromuscular block is *enhanced* by cholinesterase inhibitors and only partially reversed by calcium (table I).

TABLE I. *Reversibility of neuromuscular block. (Anti-CHE = anticholinesterases; 4-AP = 4-aminopyridine; GMA = germine monoacetate; SUX = suxamethonium; (I) and (II) = phase I and phase II; PXB = polymyxin B; + + + and + + + +: complete reversal achievable, + + + + more readily than + + +; + + + + +: overshoot)*

	Anti-CHE	Calcium	4-AP	GMA
Curariform	+ + + +	+ + +	+ + + +	+ + + + +
SUX (I)	− −	− −	−, 0	+ + + + +
SUX (II)	+ +	+ +	+ + +, ?	+ + + + +
Neomycin	+ + +	+ + +	+ + + +	+ + + + +
PXB	−	+ +	+ + + +	?

Most likely, neomycin blocks neuromuscular transmission by competition with calcium at the motor nerve terminal (Pittinger and Adamson, 1972). It reduces the calcium influx into the motor nerve terminal, thereby reducing the probability of release of transmitter therefrom. It also depresses the postjunctional action of acetylcholine (Wright and Collier, 1977). *In vivo*, neomycin and magnesium have qualitatively inseparable effects on the relationship between the paired compound electromyographic responses of the muscle elicitable by double nerve stimuli. This last observation we believe confirms the specific magnesium-like prejunctional mechanism of action of neomycin *in vivo* (personal observation). By contrast, Wright and Collier (1976) have attributed the main site of neuromuscular action of polymixin B to the postjunctional membrane. Our feeling is that the neuromuscular effect may merely represent one aspect of its generalized membrane-depressive action (Lee, Ricker and Katz, 1979).

The diagnosis of antibiotic-induced neuromuscular block remains empirical and depends primarily on the history of occurrence. It is often made by the process of elimination, after failure to explain the clinical picture without implicating the antibiotics. The blood concentrations of antibiotics required to establish a block are unknown. Examination in the cat has revealed that neomycin-induced neuromuscular block is not characterized by train-of-four fade or tetanic fade, but by an absence of fade, an undiminished tetanus, and a post-tetanic exhaustion which follows a transient post-tetanic facilitation (Lee et al., 1976). These characteristics may allow for diagnosis of neomycin-induced neuromuscular block in the absence of concomitant use of curare. Obviously, antibiotics and tubocurarine block differently, and absence of train-of-four or tetanic fade is not a reliable sign of complete neuromuscular recovery in the case of antibiotic-induced paralysis. Whether the abovementioned electromyographic technique will facilitate the diagnosis has yet to be seen.

Other drugs interacting with muscle relaxants include magnesium, lithium, other electrolytes, diazepam, anti-cancer drugs, steroids, and local and general anaesthetics. Dantrolene is devoid of neuromuscular blocking activities at usual clinical doses, but it may cause muscle weakness by direct depression (see below). Drug interactions may also occur between antibiotics and between relaxants. Respiratory acidosis and hypokalaemia may enhance non-depolarizing neuromuscular block and make the block difficult to reverse. With calcium being a prerequisite for transmitter release, hypocalcaemia may theoretically potentiate neuromuscular block. However, the extent of hypocalcaemia required to do this is unclear. The patient would probably have been treated with calcium for cardiac or haematological reasons before he encountered significant problems with neuromuscular blockers. Mannitol and furosemide enhance the neuromuscular blocking effects of tubocurarine (Miller, Sohn and Matteo, 1976).

Instead of increasing paralysis, a few drug interactions may result in a less profound neuromuscular block. Following pretreatment with a small dose of non-depolarizing blocker for the purpose of preventing suxamethonium-induced fasciculation, a larger dose of suxamethonium will be required to produce a given degree of block. Then, when a larger dose of suxamethonium is used, the resultant paralysis may be somewhat prolonged. Azathioprine (Dretchen et al., 1976), theophylline (Doll and Rosenberg, 1979) and caffeine (personal observation) antagonize non-depolarizing neuromuscular block, probably by inhibition of phosphodiesterase in the motor nerve terminal, thereby increasing the output of transmitter.

Muscle relaxants in paediatric and morbidly obese patients

Recent reports strongly suggest that reasonably healthy small infants may be more resistant rather than more sensitive to pancuronium (Goudsouzian, Ryan and Savarese, 1974), tubocurarine (Goudsouzian et al., 1975) and suxamethonium (Cook and Fischer, 1975). The popular legendary notion that young infants are very sensitive to tubocurarine may represent anecdotes of pathologically sensitive responses of the few very sick infants who may be hypothermic, hypoxic, dehydrated, acidotic and hypocalcaemic.

Is mg kg^{-1} or mg m^{-2} a better basis for dose determination of curariform drugs? The morbidly obese adult patients require a greater total, but a normal mg m^{-2} dose of pancuronium (Tseuda et al., 1978). Obviously, one should use special caution when paralysing these patients. Few children are morbidly obese. In general they do well with an mg kg^{-1} schedule, which can be determined more accurately and readily.

Passage of muscle relaxants into the cerebrospinal fluid

Non-depolarizing neuromuscular blockers injected into the cerebrospinal fluid in the lateral cerebral ventricle have dual effects in dogs. A small dose of tubocurarine (0.5 μg) induces sleep, a larger dose (2 μg) causes excitation and a still larger dose (25 μg) causes convulsions (Haranath and Shyamalakumari, 1973). Accidental injection of gallamine into the spinal fluid resulted in prolonged seizures in man (Goonewardene et al., 1975). In the rhesus monkey, a neuromuscular blocking dose of gallamine increases the lignocaine seizure threshold (Munson and Wagman, 1973).

It appears certain that neuromuscular blockers do cross the blood–brain barrier under normal circumstances, but only in amounts insufficient to have clinical significance. In man, a neuromuscular blocking dose of tubocurarine injected i.v. produces in the cerebrospinal fluid a concentration of 3.5–24.9 ng ml^{-1} (Matteo et al., 1977). In man and in dog, a neuromuscular blocking dose of gallamine injected i.v. leads to it appearing in the cerebrospinal fluid. The concentration in the cerebrospinal fluid reaches up to an equivalent of 0.75 μg ml^{-1} in man and 1 μg ml^{-1} in dog (Haranath et al., 1973). Whether an impaired blood–brain barrier increases the passage and whether the increased passage may be of neural consequence are unclear.

MONITORING AND REVERSAL OF CURARIFORM BLOCK

Individual variability in neuromuscular response

The individual variability in response to a given dose of neuromuscular blocker is well known. Tubocurarine 0.1 mg kg^{-1} given i.v. may produce no depression of the thumb twitch at all in about 6% of patients, but a total block in another 7% (Katz, 1967a). Such a wide variation in response cannot be totally explained by the variation in the serum concentration of the neuromuscular blocker. Even with the same serum concentration, the magnitude of block may differ. Among normal subjects, the serum concentration required for a given degree of block may vary as much as four-fold, as is evident from the data of Matteo, Spector and Horowitz (1974). Furthermore, changing physical conditions may result in changing neuromuscular sensitivity in the same patient, even in the same session. Controlled paralysis therefore requires individual treatment of the patient, which in turn requires close monitoring.

Purpose of monitoring

Monitoring serves to diagnose, quantify and differentiate among types of neuromuscular block, and to differentiate central from peripheral causes of apnoea. The techniques make it possible to meet the individual needs of patients for relaxation, without undue risk of failing to terminate the block when indicated.

Monitoring without nerve stimulation

Well-known criteria for adquate neuromuscular recovery include the ability to lift the head off the table for 5 or 10 s, the ability to generate an adequate negative pressure against an occluded airway, adequate respiratory parameters, and others such as a sustained strong hand squeeze, wide-open eyes, tight sternocleidomastoides, the absence of nystagmus, breathing without rocking movement of the chest or jaw retraction, co-ordinated and effective swallowing, normal voice, etc. A keen observer can often make a diagnosis at a glance. For example, a small infant or young child in a strange environment will always open the eyes when awake and able to do so. Since eye-opening is a sustained tetanus, and eyelids are among the most sensitive to neuromuscular block, in children wide-open eyes alone are signs of virtual absence of neuromuscular block. During the course of anaesthesia, however, it is not always wise, or possible, but is sometimes dangerous to perform some of these tests; nor is it wise to wait until the end of surgery to find out about the patient's state of neuromuscular transmission and the reversibility of the block.

How to stimulate the nerve

Use *supramaximal stimuli* to ensure activation of all the axons in the nerve. A submaximal stimulus is undesirable for monitoring neuromuscular transmission because the muscle response to submaximal stimulation depends not only on the state of neuromuscular transmission, but also on the number of axons activated. Nerve stimulators ("monitors") marketed for clinical use may not deliver sufficient current to the nerve for supramaximal stimulation, particularly if the jelly electrode pads are used in an attempt to stimulate through the thick, hairy and greasy skin. Conductive needles placed subcutaneously are more reliable. Constant current stimulators are also advantageous, as opposed to constant voltage stimulators: both electrodes should be placed near the nerve (but avoiding cutting the nerve with the needles), in the direction of the nerve, close to each other to increase the current density between the electrodes, and one on each side of the nerve to avoid missing the nerve. Neuromuscular transmission should be quantified by the muscle response to supramaximal stimulation, but not by the stimulus intensity required for a given response.

Most published criteria of relaxation and reversal are based on the "thumb twitch". When the hand is not available, the peroneal nerve may be stimulated for the twitch of the foot, or the facial nerve may be stimulated for the twitch of the face (especially of the orbicularis oculi). The little finger and the facial muscles are more likely to move as a result of direct muscle stimulation. To prevent this, excessive stimulus intensity should be avoided, and stimulation should be where the facial nerve enters the face and not where the muscles are. Irrelevant muscle movement should be ignored.

Mechanomyographic and electromyographic monitoring

The muscle response can be quantified by inspection, by palpation, or more exactly by mechanomyographic or electromyographic analysis. Recording of the mechanomyographic response requires secure stereotactic positioning of the force transducer. Otherwise it may not be worth the trouble, being unnecessary for practical use, but not exacting enough for accurate quantification. For a brief account of the electromyographic technique, see below.

The single twitch

A single twitch properly evoked, such as that evoked with a short (0.2 ms) square electric pulse of supramaximal intensity, remains the standard to which reference is made in quantification of neuromuscular block. For example, a 50% block of neuromuscular transmission refers to a 50% depression of *the single twitch.* To be precise, such a standard twitch ("the twitch") should be *unconditioned*, that is unpreceded by a tetanus or by another twitch. A conditioned twitch has markedly different sensitivity, as will be explained below.

Fade of train of twitches

Without neuromuscular block, a twitch conditioned by another twitch within the preceding 10 s (but beyond the refractory period of 6–7 ms) tends to become slightly greater. With curariform block, a twitch preceded by another within 10 s will be further depressed (fig. 2).

If, during partial neuromuscular block, the nerve-muscle preparation is *continually stimulated* at a frequency greater than 0.1 Hz, the degree of block will appear to be greater than it really is (if stimulated at a frequency less than 0.1 Hz). This is stimulus

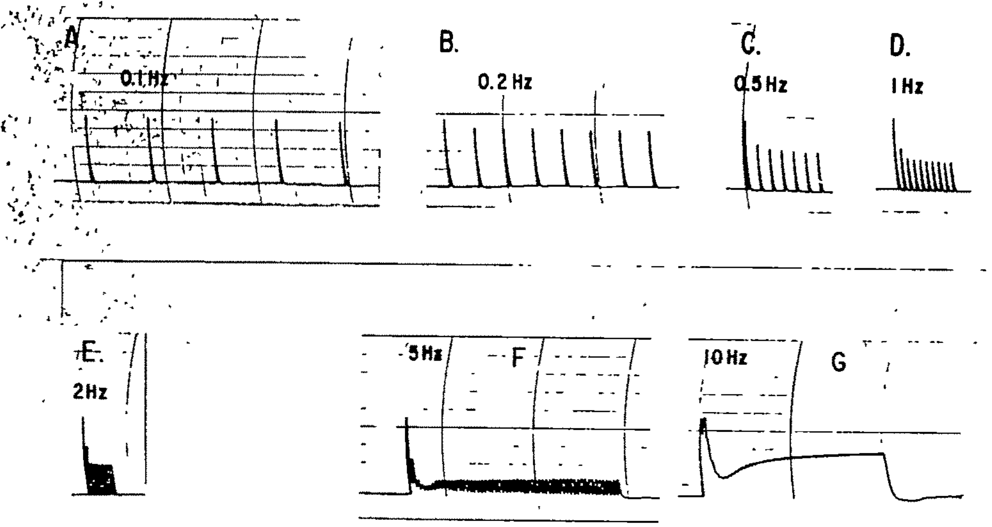


FIG. 2. Stimulus frequency, fade and curariform block. Tracings were recorded during partial neuromuscular block in a clinical setting. Twitches 10 s apart (A), and the first of each train of twitches elicited at greater frequencies (B to G), are virtually unconditioned. Their amplitude depends only on the magnitude of block at the moment. The magnitude of fade increases and the magnitude of the stabilized faded responses decreases with the increasing stimulus frequency, but maximal fade occurs with 2 Hz, E (without fusion of twitches), or with 5 Hz, F (with partial tetanization). Irrespective of stimulus frequency, four twitches are necessary and sufficient to reveal the fade totally, in the absence of tetanization.

frequency dependence of neuromuscular sensitivity. Meanwhile, if a stimulus frequency greater than 0.1 Hz is *first introduced* during curariform block, the new train of responses will decline rapidly, the second weaker than the first, the third weaker than the second, and so on (fig. 2). This is *fade*. Only the first twitch of the train is unconditioned. The extent of diminution of the subsequent (conditioned) responses depends on the stimulus frequency and the magnitude of block (Ali, Utting and Gray, 1970; Ali and Savarese, 1976). After the initial rapid decline, the train of responses tends to be stabilized again, recover slightly before it becomes stabilized, or continue to decline at a reduced rate (fig. 2). We propose that only the initial decline be called fade.

Tetanus

If the stimulus frequency exceeds 5 Hz, the thumb begins to fail to return to the relaxed resting state between twitches (fig. 2). This is partial tetanization. At 20–30 Hz and more, the mechanical response becomes completely fused (tetanization). The tetanic force of the muscle at any moment is the sum of the mechanical response to a number of action potentials in the preceding period, the electrical amplitude of each of which can be analysed individually by electromyogram.

In examining the tetanic response, stress should be given to the initial rapid decline (*fade*) which is characteristic of curariform block. After the initial fade, which occurs within 0.5 s, the tetanus may show partial recovery before it decays again. The secondary more gradual decay in tetanic response (*fatigue, exhaustion*) is non-specific and can be demonstrated with any type of neuromuscular block and in normal subjects. The greater the stimulus frequency and the longer the tetanic stimulation is applied, the less specific it becomes. While a long continued high frequency tetanic stimulation will no doubt demonstrate with increased sensitivity a minimal residual curariform block, a 30–50 Hz tetanus of a short duration appears preferable for clinical monitoring because it is more relevant to the patient's well-being and more specific to curariform block. To ascertain the absence of tetanic fade, attempt should be made to push the patient's hand back while the tetanic stimulation is applied. Some anaesthetists can quantitate the tetanic force and tetanic fade more easily by palpation than by sight.

Post-tetanic twitch

A twitch conditioned by a preceding tetanus is greatly augmented (*post-tetanic facilitation*). This is a physiological phenomenon which occurs in the absence of neuromuscular block (Katz, 1973). Mechanomyographically the post-tetanic twitch is normally up to two to three times as forceful, depending on the muscle, the species, the tetanus and the post-tetanic time course. The mechanical facilitation observed is a muscle rather than a neuromuscular phenomenon and is not seen in the electromyogram, which is an electrical response. Thus there is a dissociation of electrical and mechanical response with the mechanical response facilitated, but not the electrical response. Curariform block makes the post-tetanic augmentation of twitch response even more observable. Then the facilitation occurs both in the mechanical and electrical responses. Each tetanus distorts the post-tetanic state of neuromuscular transmission for at least 5 min, sometimes up to 30 min. Thus repeated unnecessary tetanus will give a false picture of the degree of neuromuscular block with recovery appearing to be more rapid than it really is.

Train-of-four, train-of-four fade, train-of-four ratio and train-of-four count

To quantify fade and to use fade to quantify neuromuscular block, a train of four twitches can be elicited (Ali, Utting and Gray, 1970, 1971). As can be seen from figure 2, the most efficient train consists of four twitches elicited with 0.5 s between the neighbouring twitches (that is, at 2 Hz). This is the standard *train-of-four*. It should be pointed out that the first twitch in the train is in itself an unconditioned twitch, has all the advantages of the single twitch, and qualifies as the reference twitch, if and only if it is not preceded by any other nerve stimulation for approximately 10 s, or more. Train-of-four lacks the equivalent of post-tetanic distortion of the subsequent muscle response, and is therefore suitable for repeated application, up to once every 12 s.

The practical uses of train-of-four in the monitoring of curariform block are summarized in figures 3 and 4.

In addition, if the four twitches fade enough for the fade to be visible just by looking at the fingers, the state of neuromuscular transmission is below point B in figures 3 and 4; in other words, there exists some block of the single twitch (personal observation). An individual's dose requirement of curariform drug for a just visible train-of-four fade, which corresponds to the threshold blocking dose for the single twitch, predicts the same individual's dose requirement. A 50% and a 95% block requires two times and three times this threshold-block dose, respectively (Savarese, personal communication). On the other hand, if the train-of-four ratio has recovered to 0.75 or greater (that is, above point B in figures 3 and 4), an otherwise fit individual will have sufficient respiratory neuromuscular reserve (Ali et al., 1975). As a corollary, adequate respiratory reserve requires 100% recovery of the single twitch. If an individual's train-of-four fades enough for the fade to be visible just by

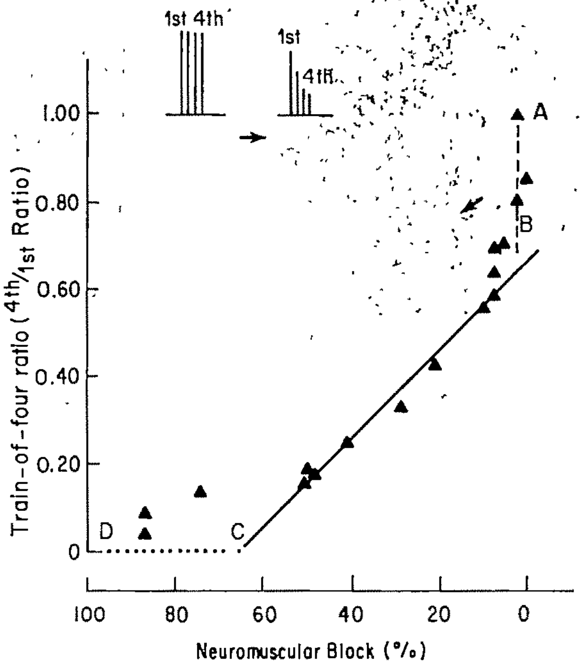


FIG. 3. Relationship between train-of-four ratio and magnitude of curariform block. From A to B, before neuromuscular block begins to depress the first twitch, the fourth twitch will be depressed to 75% of control and the train-of-four (4th/1st) ratio will be reduced to 0.75 from 1. From B to C, as neuromuscular block (defined as diminution of the first twitch) increases from 0% to the vicinity of 75%, the train-of-four ratio diminishes further, from 0.75 to zero. It is possible to estimate the magnitude of block without referring to the control response by determination of the train-of-four ratio, because there exists an apparently linear relationship between these two variables (Ali, Utting and Gray, 1970; 1971). This requires considerable instrumentation. From C to D, train-of-four ratio remains zero. As the first twitch is depressed further, from 75% block to total block, the number of residual twitches one can count out of the four will diminish from 4 to zero, as will be shown in figure 4. Points in this figure were taken from a patient in a clinical setting.

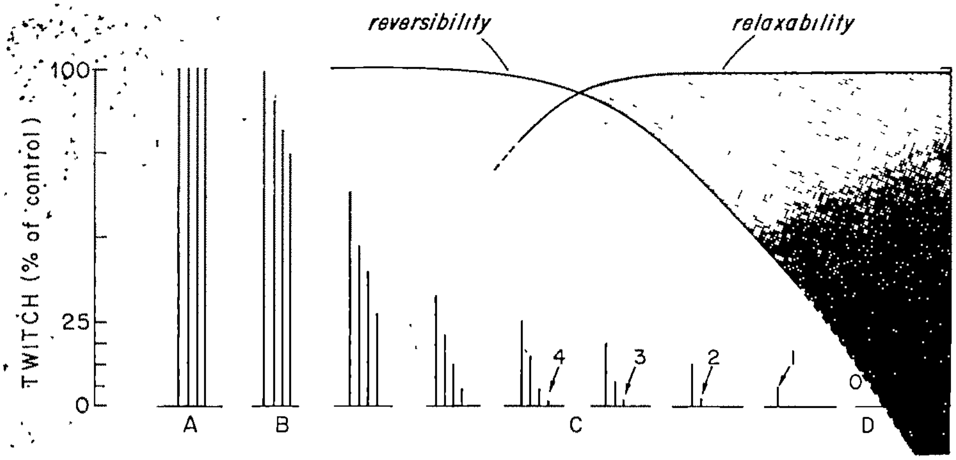


FIG. 4. "Train-of-four count", relaxability and reversibility of curariform block. A, B, C and D correspond to the equivalent points labelled with the same letters in figure 3. After the train-of-four ratio becomes zero, C, disappearance of the 4th twitch is followed by disappearance of the 3rd, the 2nd and finally the 1st twitch, as neuromuscular block (measured as diminution of the first twitch) progresses from 75% block to total block. Regarding relaxability, an 80% block should provide satisfactory abdominal relaxation, provided adequate anaesthesia and a clear airway are maintained (Katz, 1967a, 1971). Regarding reversibility, the difficulty to reverse the block will increase rapidly, as shown by the rapidly declining reversibility curve, if the block is more profound than 80% depression of the twitch, as can be seen from figure 5, it may become very difficult (Baraka, 1967), beyond point D. To assess both profound block and reversibility, in the "grey zone" between C to D, use the "train-of-four count", 4, 3, 2, 1 and 0 as shown.

looking at the fingers, that individual has a train-of-four ratio below 0.75, and probably needs respiratory support, unless the block can be reversed.

Relaxability and reversibility of curariform block

With tubocurarine (Katz, 1967a) as with pancuronium (Katz, 1971), spontaneous recovery to approximately 20% of the initial response (80% residual block) should allow for rapid and complete reversal of neuromuscular transmission by anticholinesterases in approximately 10 min (fig. 5). A block more profound than 80% (up to 90–95%) can still be reversed, as long as all four twitches of the train-of-four are not eliminated. A larger dose of anticholinesterase (up to 5 mg of neostigmine, for example) and a longer time (up to 30 min, for example) may be required. It has been pointed out that the percentage of block (referring to the single twitch) at which the block is profound enough for the train-of-four twitches to disappear (one by one) may vary. Nevertheless, the "train-of-four count" (Lee, 1975b) by itself offers a method of quantitation of curariform block in stages, to cover a "grey" zone of profound block which borders on loss of reversibility (figures 4 and 5). A common mistake made in the attempt to

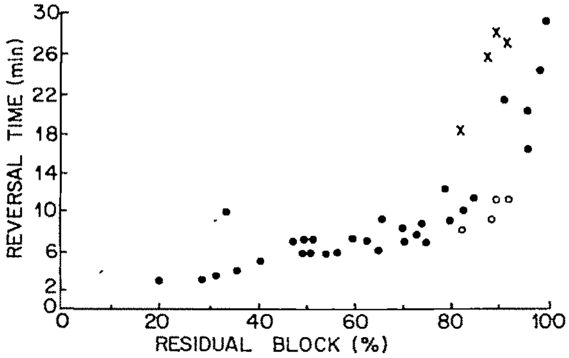


FIG. 5. Time requirement of reversal of pancuronium-induced neuromuscular block. The more profound the residual block is, the more difficult it is to reverse the block, especially if the residual block exceeds 80%. This point of rapidly increasing difficulty corresponds approximately to point C in figures 3 and 4. It can be avoided if all four twitches of the train-of-four are present. Circles and crosses indicate four patients, each of whom received pancuronium on two separate occasions, and was reversed from the same point of residual block on both occasions. In each one of them, reversal was more promptly achieved on the occasion when more time had elapsed since the last dose of pancuronium was given (modified from Katz, 1971).

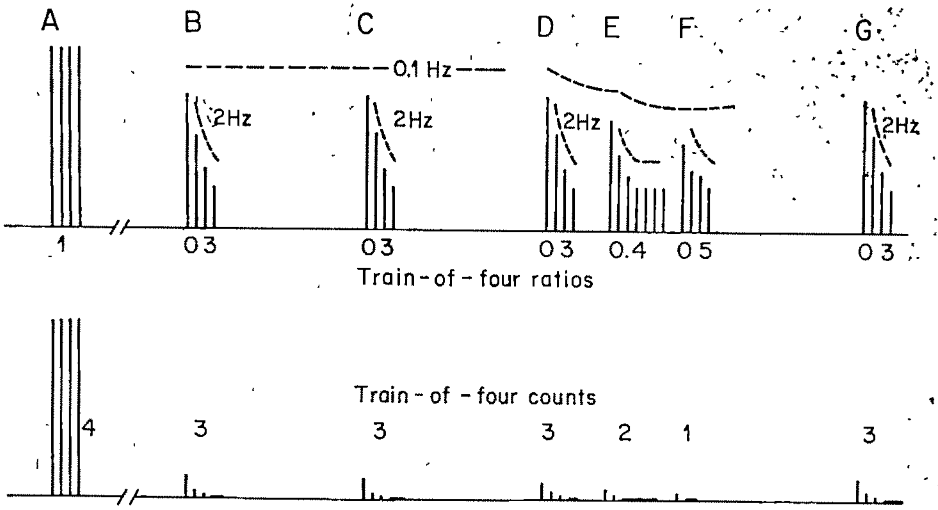


FIG. 6. A common source of error in using the train-of-four methods is failure to let the nerve–muscle preparation recover between applications of stimulation. To the left are control responses. Upper panel: 25% curariform block, with a correct train-of-four ratio of 0.3. Responses in columns B, C, D and G have the correct ratio, because their first twitches are not preceded too closely by another stimulation. Columns E and F have their first twitches already faded because their first twitches, being already pre-conditioned by a closely spaced twitch, are in fact the second and third twitches of another fading train DEF. (Any train repeated at a faster rate than 0.1 Hz will fade, see figure 2.) Lower panel: 88% block, with a correct train-of-four count of 3. Note failure to provide a 10-s rest will result in a high train-of-four ratio (0.4, 0.5) which under-estimates, but a low train-of-four count (2,1) which over-estimates the magnitude of block. The reason is that if the stimuli are repeated at 2 Hz indefinitely, the twitches will eventually be depressed by 75% in the presence of a 25% block, or disappear in the presence of an 88% block, as illustrated in E, where seven twitches are shown to represent a long train. To restore the correct train-of-four, let the nerve–muscle preparation rest for 10 s, column G. (Numbers in this diagram are only estimates.)

utilize the "train-of-four", and an easy remedy for the mistake, are illustrated in figure 6.

Calculated trespasses

Beyond the point of 100% block of the twitch, there is a zone of minimal residual neuromuscular transmission. The tetanus is normally stronger than the single twitch and so is the post-tetanic twitch. When the single twitch is no longer elicitable, because of profound block, presence of some residual tetanus or post-tetanic twitch indicates that spontaneous recovery of neuromuscular transmission to the point of reversibility is still in sight.

Correlation between neuromuscular block, relaxation and muscle power

Without nerve impulses, normal muscles are relaxed. On the other hand, strong nerve drive will make it difficult to relax the muscle.

For example, a 95% curariform block of the twitch may be equivalent to an 80% diminution of the tetanus (Lee, Barnes and Katz, 1976). The remaining 20% tetanus may be translated into several kilograms of force in the respiratory musculature, which may be bothersome during operation if hiccup, cough reflex or strong respiratory drive stimulate the diaphragm into maximal tetanic response. Adequate anaesthesia, a clear airway, proper ventilation and a gentle operating technique make it possible to produce a relaxed and quiet operating field with no more than an easily reversible block. Obviously, adipose tissue, contractured joints and muscle response to direct stimulation cannot be "relaxed" by neuromuscular blockers.

For monitoring of depolarizing block and phase II block, see below. For additional information on monitoring of neuromuscular function see Ali and Savarese (1976). A brief summary of the reversibility of various types of neuromuscular block has appeared in table I. A more detailed account of the reversal of neuromuscular block has been published by Miller (1976).

TABLE II. *Characteristics of neuromuscular block produced by drugs acting with different mechanisms of action. Values are relative, and approximate, 100 referring to 100% of the control twitch response. Characteristics of block observed at 50% block of the twitch produced by various blocking agents are represented numerically. Table shows that different neuromuscular blocking agents depress the various parameters of neuromuscular function with different sensitivity profiles. It is often too simplistic and too arbitrary to describe a neuromuscular blocker as either fading or non-fading. Instead, descriptive neuromuscular pharmacology should be studied in quantitative terms, whenever possible*

	Twitch	Train-of-four	Tetanus	Post-tetanic response
Normal	100	100 → 100	500 → 500	250 → 125 → 100
Tubocurarine	50	50 → 10	300 → 100	200 → 100 → 75
SUX (I)	50	50 → 50	150 → 150	60 → 50 → 50
SUX (II)	50	50 → 20	300 → 150	150 → 100 → 75
α-BuTX	50	50 → 50	300 → 300	200 → 100 → 40
Neomycin	50	50 → 50	500 → 500	250 → 20 → 75
PXB	50	50 → 30	300 → 250	200 → 100 → 75

PHENOMENOLOGY OF NEUROMUSCULAR BLOCK

The correlation between the observed characteristics of block and the proposed mechanisms of action has been the subject of several recent investigations. While tubocurarine-induced neuromuscular block is characterized by fade of tetanus and train-of-four, as well as post-tetanic augmentation of the twitch response, these signs are not common to all "non-depolarizing" block. First of all, post-tetanic facilitation is a physiological phenomenon as discussed above. Alpha-bungarotoxin, a model "permanent" postjunctional neuromuscular blocker, blocks without causing tetanic or train-of-four fade (Lee, Chen and Katz, 1977). Pancuronium does not always cause marked tetanic fade either (Bowman and Webb, 1976). Fade of tetanus may well be indicative of the prejunctional effect of curariform drugs (Bowman and Webb, 1976). However, not all drugs acting prejunctionally will cause fade. For example, neomycin-induced neuromuscular block manifests other signs of prejunctional block, but not tetanic or train-of-four fade. Post-tetanic augmentation of twitch response of the soleus in the absence of neuromuscular block may originate prejunctionally, while that of the gastrocnemius is a postjunctional phenomenon (Standaert, 1964). Suxamethonium specifically depresses the post-tetanic augmentation (personal observation). Table II is a summary of the commonly observed characteristics of neuromuscular block produced by blockers acting with different mechanisms of action. Further investigations are required before prejunctional neuromuscular pharmacology may become more than an academic curiosity to the clinicians. The important point we wish to make is that the textbook discussion of fade, post-tetanic facilitation and site of action of neuromuscular blockers is a gross oversimplification which, while perhaps once useful, is now an obstacle to clear understanding.

REVIEW OF EXISTING DRUGS

Non-depolarizing neuromuscular blocking agents

Many recent studies concern the autonomic and the cardiovascular side-effects of muscle relaxants. If the dose requirement for a given autonomic side-effect is much greater than the dose requirement for neuromuscular block, the side-effect probably can be avoided. The relaxant is then said to have a *wide autonomic margin of safety* (Hughes and Chapple, 1976; Savarese, 1979). Table III presents the comparative pharmacology of tubocurarine, metocurine and pancuronium.

TABLE III. *Comparative pharmacology of tubocurarine, metocurine and pancuronium* (ED_{50}, *mg* kg^{-1}, *cat*). * *Adapted from Savarese* (1979). † *Savarese, J. J. (personal communication).* ‡ *Corresponding values in humans are: tubocurarine* 0.26, *metocurine* 0.13, *pancuronium* 0.036 (*Savarese, Ali and Antonio,* 1977). § *In terms of serum concentration required* (ED_{50}, μg ml^{-1} *in humans*); *tubocurarine* 0.65 (0.1 *Hz*) *or* 0.45 (0.3 *Hz*), *metocurine* 0.35 (*R. Matteo, personal communication; Matteo, Spector and Horowitz,* 1974), *pancuronium* 0.21 (*Somogyi, Shanks and Triggs,* 1976; *Agoston et al.,* 1977)

	Tubocurarine*	Metocurine*	Pancuronium†
Neuromuscular block‡§ (tibialis anterior)	0.15	0.013	0.013
Sympathetic block (nictitating membrane)	1.35	4.40	23.0
Vagal block (vagal bradycardia)	0.29	0.85	0.20
Histamine release (delayed depressor response)	0.40	0.88	(no release)

The general pharmacological profile is clearly that tubocurarine depresses the cardiovascular functions, blocks the autonomic ganglia and releases histamine. Metocurine is least likely to have any cardiovascular effects, although it does release histamine at greater doses. Pancuronium may stimulate the sympathetic ganglionic transmission, is vagolytic ("atropine-like"), is unlikely to release histamine, and possesses sympathomimetic activities. It causes tachycardia and hypertension to various extents. Gallamine is the most vagolytic at clinical neuromuscular blocking doses. Incidentally, dimethyl-tubocurarine is now re-named metocurine because tubocurarine itself is a monoquaternary instead of a bisquaternary compound as previously thought. Generally speaking, metocurine is between tubocurarine and pancuronium in most aspects.

In addition to vagolysis, pancuronium accelerates atrio-ventricular conduction (Geha et al., 1977), blocks the re-uptake of noradrenaline (Ivankovich et al., 1975), increases heart rate, arterial pressure and cardiac output without altering the total peripheral resistance (Kelman and Kennedy, 1971), and increases the vascular tone of the capacitance vessels under certain circumstances (personal observation). However, pancuronium has little effect on myocardial contractility (Duke, Fung and Gartner, 1975). It exerts its cardiovascular effects primarily by blocking the muscarinic receptors in the heart.

Anti-cholinesterase antagonists and anticholinergic drugs

Pyridostigmine is well accepted as an alternative to neostigmine (McNall et al., 1969). It has less autonomic side-effects (Katz, 1967b) than neostigmine, produces fewer arrhythmias in elderly patients (Owens, Waldbaum and Stephen, 1978) and may be of special value in anephric patients. Whether its longer duration of action is a significant advantage in patients with normal renal function is not clear. Patients with normal kidneys and liver who receive a moderate dose of curariform drug do not require the prolonged action of pyridostigmine. Once completely reversed, neuromuscular block produced by the curariform drugs rarely recurs, even in patients without renal or hepatic function. Cholinesterase inhibitors, like the neuromuscular blocking agents, also have a longer duration of action in the absence of renal function (see above). Furthermore, having the cholinesterase inhibitors outlast the anticholinergics (atropine or glycopyrrolate) or the neuromuscular blocker is not beneficial. *Physostigmine* has also been well accepted into anaesthesia practice, as a reversal agent, not for neuromuscular block, but for c.n.s. depression.

Glycopyrrolate is a quaternary ammonium anticholinergic compound which is at least as potent as the tertiary compound atropine in antisialagogic action. At equi-antisialagogic dose it causes less tachycardia than atropine does, but prevents the bradycardic effect of neostigmine as effectively (Ramamurthy, Ylagan and Winnie, 1971; Wyant and Kao, 1974). An additional advantage may include more effective reduction of acidic gastric secretion. It may also possess less c.n.s. effect, because quaternary ammonium compounds do not cross the blood–brain barrier readily (Proakis and Harris, 1978).

Suxamethonium and train-of-four in phase II block

Suxamethonium remains one of the most useful drugs in anaesthesia. Some major advantages keep it

TABLE IV. *Disadvantages of suxamethonium (classified by mechanism)*

- Depolarization:
  - Muscle pain
  - Fasciculation
    - Increase of intra-gastric and intra-cranial pressures
    - Fracture of osteoporotic bones (?)
  - Contracture
    - Denervated or dystrophic muscles
    - Extra-ocular muscle spasm
      - intra-ocular hypertension
      - extrusion of contents of open eye
  - Potassium efflux, hyperkalaemia, cardiac consequences
    - Minimal effects in normal subjects
    - Cardiac irregularities or arrest in patients with:
      - burns and massive trauma
      - major central or peripheral nervous system lesions
      - renal failure with existing hyperkalaemia
      - neuromuscular degeneration

- Changing nature of block:
  - Tachyphylaxis
  - Prolonged block in phase II (?)

- Other agonistic actions:
  - Tachycardia and hypertension
  - Sinus bradycardia and arrest, vago–vagal reflex

- Idiosyncratic responses:
  - Atypical plasma cholinesterase and prolonged block
  - Other genetic abnormalities
  - Malignant hyperthermia

- Active metabolites:
  - Contributory to prolonged block (?)

- Drug interactions:
  - Cholinesterase inhibitors (eye drops)—prolonged block
  - Digitalis—cardiac arrhythmia (?)

in continuous demand despite a multitude of potentially serious disadvantages (table IV). Many of these complications arise directly or indirectly from its depolarizing mechanism of action. Philosophically, a block produced by a rapid and massive depolarization is rarely a sound basis of therapeutics in medicine. The main advantages of suxamethonium are the short duration of action, the lack of tissue toxicity and the absence of intolerable cardiovascular side-effects in most patients.

Theoretically, a short duration of action is a sound basis for prolonged use of drugs in anaesthetic practice, because it ensures rapid recovery. In the case of suxamethonium, however, prolonged use leads to emergence of a different type of block which is neither short-acting nor readily reversible. For recent laboratory investigations on the changing nature of suxamethonium-induced neuromuscular block see Galindo and Kennedy (1974) and Waud and Waud (1975).

The train-of-four has been used in the clinical investigations of phase II block. In phase I, the train-of-four fades minimally, and the train-of-four ratio remains relatively constant, fluctuating above 0.6–0.7. As long as the train-of-four ratio remains greater than 0.6–0.7, the block is enhanced by edrophonium. With continuous exposure to suxamethonium, the train-of-four ratio decreases, not linearly but following a sigmoid curve. A transitional period of rapidly decreasing train-of-four ratio serves to divide phase I and phase II. During the transition, tachyphylaxis occurs. In phase II, the train-of-four ratio again remains relatively constant, fluctuating below 0.3–0.4. The block becomes reversible with edrophonium, although not necessarily completely so (Lee, 1975a, 1976a). Self-antagonism can be demonstrated by bolus injection of a small dose of suxamethonium to reverse, transiently (and partially), an existing phase II block (Lee, 1976b). If the use of suxamethonium is continued further, a full recovery of the thumb twitch may be markedly prolonged, but only after phase II block has been well established according to the train-of-four criterion. Whether the development of a phase II block or the dose and time of suxamethonium administration is more important for the development of a prolonged response is still the subject of debate. In most clinical situations it is not possible to separate these factors. In practical terms, as long as the use of suxamethonium is terminated shortly after train-of-four fade is clearly established, rapid recovery of neuromuscular transmission will follow. Interestingly, patients with atypical plasma cholinesterase will emerge from the "usual dose" of suxamethonium (which is in reality an overdose to them) also with a marked train-of-four fade (Savarese et al., 1975). It should be understood that the train-of-four ratio depends not only on the nature of block, but also on the magnitude of block. The above-mentioned train-of-four criteria are based on measurements of the train-of-four ratio at the level of 50–60% block. Table V summarizes the changing nature of suxamethonium-induced neuromuscular block.

WHAT IS IN THE NEAR FUTURE?

New neuromuscular blocking agents?

The most commonly used neuromuscular blockers in current anaesthesia practice in the U.S.A. are suxamethonium, tubocurarine, metocurine and pancuronium. Any careful examination of the advantages and disadvantages of these blockers will lead to the obvious conclusion that a "non-depolarizing suxamethonium" or a "short-acting metocurine" would represent major improvements. A "pancuronium without cardiovascular side-effects" would also be a significant improvement.

To create a "non-depolarizing suxamethonium", bulky cholines have been joined to bulky di-acids to make bulky *di-esters* (Savarese et al., 1973). The principle is to replace the smaller choline and di-acid structures of suxamethonium, which account for its depolarizing action, with bulky structures. These compounds may be short-acting because they are hydrolysable by the plasma cholinesterase, as is suxamethonium. They may be non-depolarizing by virtue of the bulky rigid molecular structures. A compound, code-named AA-136 (BWY-100), had promising results in animal studies, but caused hypertension, was not readily reversed with cholinesterase inhibitors, and was not as short-acting as desired in man. Subsequently, another short-acting compound HH-110 and an intermediate-acting analogue HH-109 have been synthetized. These compounds have no significant cardiovascular side-effects in laboratory animals, are hydrolysable by plasma cholinesterase, and the block is reversible by cholinesterase inhibitors. The metabolites are much weaker than the original compound. Clinical trial of the short-acting compound is pending (J. J. Savarese, personal communication).

Another promising new muscle relaxant, code-name Org. NC-45, is one of a series of *modified pancuronium compounds*. By changing the quaternary ammonium structure on the ring 1 of the steroid

TABLE V. *The changing nature of suxamethonium-induced neuromuscular block.* † *measured at approximately 60% block.* * +, ++, +++ = *increasing twitch*; −, − − = *increasing block, semiquantitatively.* ** *Occurrence of phase II block is also dependent on duration of block, as under clinical circumstances, total dose administered increases approximately in proportion to the duration of administration. Inhalation anaesthetics appear to reduce the dose requirement of phase II block in humans*

	Phase I	Transition	Phase II
Action	depolarization	mixed	desensitization
Fasciculation	yes	unclear	no
Tetanus	no fade	equivocal	fade
Post-/pre-tetanic twitch	1	1–2	2 or more
Train-of-four	minimal fade	intermediate	maximal fade
Train-of-four ratio†	>0.7	0.4–0.7	<0.4
Edrophonium*	− −, −	−, 0, +	+, ++, +++
Tachyphylaxis	not observed	observed	cumulative effect
Self-antagonism	non-observable	equivocal	observable
Recovery	rapid	rapid	rapid (early) slow (late)
Dose requirements ($mg\ kg^{-1}$)**	2–3	4–5	6 or more

nucleus to tertiary, the cardiovascular side-effects of pancuronium are eliminated. No advantages of pancuronium are sacrificed. In addition, the monoquaternary compound may be somewhat shorter-acting than is pancuronium in man (N. Durant, D. Savage and J. Crul, personal communications). Clinical trials are in progress.

New reversal agents?

Two compounds, germine monoacetate (GMA) and 4-aminopyridine (4-AP), are potentially useful as new reversal agents. Neither is a cholinesterase inhibitor. Both are long-acting. Both may reverse blocks which cholinesterase inhibitors have failed to reverse, or produce reversal beyond the limit of effect of the cholinesterase inhibitors. They may not require atropine to counteract the side-effects. Combined use with cholinesterase inhibitors may further enhance their potential usefulness. GMA has had limited clinical trial in the treatment of myasthenia gravis (Flacke, 1973) and in the reversal of depolarizing and non-depolarizing agents. 4-AP has been used clinically with success in the reversal of curariform neuromuscular block (Stoyanov et al., 1976), and experimentally with success in the reversal of neuromuscular block produced by polymixin B and other antibiotics (Lee, de Silva and Katz, 1978; Burkett et al., 1979). It potentiates the effects of neostigmine and pyridostigmine (Miller et al., 1979). It has also been used in the reversal of ganglion block produced by hexamethonium and tubocurarine in the cat (N. Durant, C. Lee and R. L. Katz, personal observation).

New monitoring techniques?

Neurally evoked compound electromyographic response of the muscle (ncEMG) may be used to monitor neuromuscular transmission (Epstein and Epstein, 1975; Katz, 1973; Lee et al., 1977). Its major advantages over the mechanomyographic method include the provisions for detailed analysis of the tetanic fade and the refractoriness of neuromuscular transmission, and for differential diagnosis between neuromuscular block and direct muscle depression. One example of the latter is that dantrolene, which blocks the excitation–contraction coupling of the muscle without blocking neuromuscular transmission (Nott and Bowman, 1974; Morgan and Bryant, 1977), depresses the mechanical force output of the muscle without reducing the amplitude of the ncEMG (fig. 7). Technically, the instrument required for the electromyographic analysis is more difficult to adapt to daily anaesthetic use, but once a suitable instrument is available, it will be easier and quicker to monitor neuromuscular transmission electromyographically than mechanomyographically. The electromyograph will work equally well even in patients whose hands are positioned out of reach of the anaesthetists and where the correct positioning of the force transducer is impossible. A practical solution to the technical problems has been described (Lee et al., 1977). It should be remembered, as pointed out above, that the electromyographic and mechanomyographic responses may differ, the example used above being the post-tetanic response of the unparalysed muscle (Katz, 1973; Epstein and Epstein, 1975).

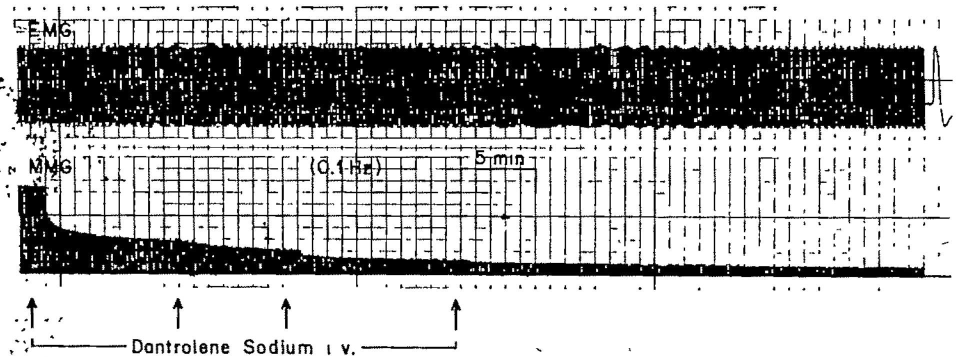


FIG. 7. Mechanomyographic (MMG) effect of dantrolene sodium in the cat. Nerve stimulation was repeated at 0.1 Hz. Dantrolene does not depress the compound electromyographic (EMG) response to nerve stimulation (upper panel) but reduces the mechanical force output of the muscle (lower panel). Neuromuscular transmission was not depressed, because the nerve impulse was successfully transmitted across the neuromuscular junction to elicit the action potential of the muscle. Excitation–contraction uncoupling prevented the mechanical performance of the muscle. The figure was produced from a cat to illustrate that neurally evoked compound EMG is more specific to neuromuscular transmission than is the mechanical response, and may aid in differential diagnosis of dantrolene-induced muscle depression from neuromuscular block. Both panels were taken simultaneously from the same muscle, tibialis anterior.

The spontaneous electromyogram of the abdominal muscles (not neurally evoked but c.n.s.-initiated) monitors the abdominal muscle tone. Irrespective of whether neuromuscular transmission is blocked, the actual muscle tone is of direct concern to the anaesthetists. However, failure to differentiate neuromuscular block from central depression and the technical difficulties of monitoring the abdominal electromyogram have prevented its wide acceptance. Another electromyographic technique, the frequency sweep electromyogram, samples the neuromuscular response to nerve stimuli of a whole range of frequencies at one sweep (Gerber et al., 1977). The sweep produces a "fade" of its own kind during curariform block, which is different from the fade described in "Monitoring and reversal of curariform block". The pharmacological meaning and the clinical significance of this interesting technique await further elucidation.

ACKNOWLEDGEMENT

The authors are indebted to Weishi Chian Lee, M.D. for her generous voluntary assistance in the preparation of the manuscript.

REFERENCES

Agoston, S., Crul, J. F., Kersten, U. W., and Scaf, A. H. J. (1977). Relationship of the serum concentration of pancuronium to its neuromuscular activity in man. *Anesthesiology*, **47**, 509.

Agoston, S., Vermeer, G. A., Kersten, U. W., and Meijer, D. K. F. (1973). The fate of pancuronium bromide in man. *Acta Anaesthesiol. Scand.*, **17**, 267.

Ali, H. H., and Savarese, J. J. (1976). Monitoring of neuromuscular function. *Anesthesiology*, **45**, 216.

—— Utting, J. E., and Gray, T. C. (1970). Stimulus frequency in the detection of neuromuscular block in humans. *Br. J. Anaesth.*, **42**, 967.

—— —— —— (1971). Quantitative assessment of residual antidepolarizing block (part I). *Br. J. Anaesth.*, **43**, 473.

—— Wilson, R. S., Savarese, J. J., and Kitz, R. J. (1975). The effect of tubocurarine on indirectly elicited train-of-four muscle response and respiratory measurements in humans. *Br. J. Anaesth.*, **47**, 570.

Baraka, A. (1967). Irreversible tubocurarine neuromuscular block in the human. *Br. J. Anaesth.*, **38**, 891.

Bowman, W. C., and Webb, S. N. (1976). Tetanic fade during partial transmission failure produced by non-depolarizing neuromuscular blocking drugs in the cat. *Clin. Exp. Pharmacol. Physiol.*, **3**, 545.

Burdfield, P. A., and Calvey, T. N. (1973). Plasma clearance of neostigmine and pyridostigmine in rats with ligated renal pedicles. *Eur. J. Pharmacol.*, **24**, 252.

Burkett, L., Bikhazi, G. B., Thomas, K. C. jr, Rosenthal, D. A., Wirta, M. G., and Foldes, F. F. (1979). Mutual potentiation of the neuromuscular effects of antibiotics and relaxants. *Anesth. Analg.* (*Cleve.*), **58**, 107.

Buzello, W., and Agoston, S. (1978). Pharmacokinetics of pancuronium in patients with normal and impaired renal function. *Anaesthetist*, **27**, 291.

Cook, D. R., and Fischer, C. G. (1975). Neuromuscular blocking effect of succinylcholine in infants and children. *Anesthesiology*, **42**, 662.

Doll, D. C., and Rosenberg, H. (1979). Antagonism of neuromuscular blockage by theophylline. *Anesth. Analg.* (*Cleve.*), **58**, 139.

Dretchen, K. L., Morgenroth, V. H., Standaert, F. G., and Walts, L. F. (1976). Azathioprine: effects on neuromuscular transmission. *Anesthesiology*, **45**, 604.

Duke, P. C., Fung, H., and Gartner, J. (1975). The myocardial effects of pancuronium. *Can. Anaesth. Soc. J.*, **22**, 680.

Epstein, R. M., and Epstein, R. A. (1975). Electromyography in evaluation of the response to muscle relaxants; in *Muscle Relaxants* (ed. R. L. Katz), p. 299. Amsterdam, London, New York: Excerpta Medica.

Flacke, W. (1973). Treatment of myasthenia gravis. *N. Engl. J. Med.*, **288**, 27.

Fogdall, R. P., and Miller, R. D. (1974). Prolongation of a pancuronium-induced neuromuscular blockade by clindamycin. *Anesthesiology*, **41**, 407.

Galindo, A., and Kennedy, R. (1974). Further observations on depolarizing neuromuscular block: the so-called Phase II block. *Br. J. Anaesth.*, **46**, 405.

Geha, D. G., Rozelle, B. C., Raessler, K. L., Groves, B. M., Wightman, M. A., and Blitt, C. D. (1977). Pancuronium bromide enhances atrioventricular conduction in halothane-anaesthetized dogs. *Anesthesiology*, **46**, 342.

Gerber, H. R., Johansen, S. H., Mortimer, J. T., and Yodlowski, E. (1977). Frequency sweep electromyogram and voluntary effort in volunteers after d-tubocurarine. *Anesthesiology*, **46**, 35.

Ghoneim, M. M., Kramer, S. E., Bannow, R., Pandya, H., and Routh, J. I. (1973). Binding of d-tubocurarine to plasma proteins in normal man and in patients with hepatic or renal disease. *Anesthesiology*, **39**, 410.

Gibaldi, M., Levy, G., and Hayton, W. (1972). Kinetics of the elimination and neuromuscular effect of d-tubocurarine in man. *Anesthesiology*, **36**, 213.

Goonewardene, T. W., Sentheshanmuganathan, S., Kamalanathan, S., and Kanagasunderan, R. (1975). Accidental subarachnoid injection of gallamine. A case report. *Br. J. Anaesth.*, **47**, 889.

Goudsouzian, N. G., Donlon, J. V., Savarese, J. J., and Ryan, J. F. (1975). Re-evaluation of dosage and duration of action of d-tubocurarine in the pediatric age group. *Anesthesiology*, **43**, 416.

—— Ryan, J. F., and Savarese, J. J. (1974). The neuromuscular effect of pancuronium in infants and children. *Anesthesiology*, **41**, 95.

Greenblatt, D. J., and Koch-Weser, J. (1975). Clinical pharmacokinetics: I and II. *N. Engl. J. Med.*, **293**, 702 and 964.

Ham, J., Miller, R. D., Benet, L. Z., Matteo, R. S., and Roderick, L. L. (1978). Pharmacokinetics and pharmacodynamics of d-tubocurarine during hypothermia in the cat. *Anesthesiology*, **49**, 324.

Haranath, P. S. R. K., Krishnamurty, A., Rao, L. N., and Seshagirirao, K. (1973). Passage of gallamine from blood into the liquor space in man and in dog. *Br. J. Pharmacol.*, **48**, 640.

—— Shyamalakumari, S. (1973). Sleep induced by small dose of tubocurarine injected into cerebral ventricles in dog. *Br. J. Pharmacol.*, **48**, 23.

Hashimoto, Y., Shima, T., Matsukawa, S., and Satou, M. (1978). A possible hazard of prolonged neuromuscular blockade by amikacin. *Anesthesiology*, **49**, 219.

Horowitz, P. E., and Spector, S. (1973). Determination of serum d-tubocurarine concentration by radioimmunoassay. *J. Pharmacol. Exp. Ther.*, **185**, 94.

Hug, C. C. jr. (1978). Pharmacokinetics of drugs administered intravenously. *Anesth. Analg.* (*Cleve.*), **57**, 704.

Hughes, R., and Chapple, D. J. (1976). Effects of non-depolarizing neuromuscular blocking agents on peripheral autonomic mechanisms in cats. *Br. J. Anaesth.*, **48**, 59.

Hull, C. J. (1979). Pharmacokinetics and pharmacodynamics. *Br. J. Anaesth.*, **50**, 579.

Ivankovich, A. D., Miletich, D. J., Albrecht, R. F., and Zahed, B. (1974). The effect of pancuronium on myocardial contraction and catecholamine metabolism. *J. Pharm. Pharmacol.*, **27**, 837.

Katz, R. L. (1967a). Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. *Anesthesiology*, **28**, 327.

—— (1967b). Pyridostigmine (Mestinon) as an antagonist of d-tubocurarine. *Anesthesiology*, **28**, 528.

—— (1971). Clinical neuromuscular pharmacology of pancuronium. *Anesthesiology*, **34**, 500.

—— (1973). Electromyographic and mechanical effects of suxamethonium and tubocurarine on twitch, tetanic and post-tetanic responses. *Br. J. Anaesth.*, **45**, 849.

Kelman, G. R., and Kennedy, B. R. (1971). Cardiovascular effects of pancuronium in man. *Br. J. Anaesth.*, **43**, 335.

Kersten, U. W., Meijer, D. K. F., and Agoston, S. (1973). Fluorimetric and chromatographic determination of pancuronium bromide and its metabolites in biological materials. *Clin. Chem. Acta*, **44**, 59.

Lee, C. (1975a). Dose relationship of Phase II, tachyphylaxis and train-of-four fade in suxamethonium-induced dual neuromuscular block in man. *Br. J. Anaesth.*, **47**, 841.

—— (1975b). Train-of-four quantitation of the competitive neuromuscular block. *Anesth. Analg.* (*Cleve.*), **54**, 649.

—— (1976a). Train-of-four fade and edrophonium antagonism of neuromuscular block by succinylcholine in man. *Anesth. Analg.* (*Cleve.*), **55**, 663.

—— (1976b). Self-antagonism: a possible mechanism of tachyphylaxis in suxamethonium-induced neuromuscular block in man. *Br. J. Anaesth.*, **48**, 1097.

—— Barnes, A., and Katz, R. L. (1976). Neuromuscular sensitivity to tubocurarine: a comparison of 10 parameters. *Br. J. Anaesth.*, **48**, 1045.

—— Chen, D., Barnes, A., and Nagel, E. I. (1976). Neuromuscular block by neomycin in the cat. *Can. Anaesth. Soc. J.*, **23**, 527.

—— —— Katz, R. L. (1977). Characteristics of nondepolarizing neuromuscular block: (I) Post-junctional block by alpha-bungarotoxin. *Can. Soc. Anaesth. J.*, **24**, 212.

—— Katz, R. L., Lee, A. S. J., and Glaser, B. (1977). A new instrument for continuous recording of the evoked compound electromyogram in the clinical setting. *Anesth. Analg.* (*Cleve.*), **56**, 260.

—— Ricker, S., and Katz, R. L. (1979). Autonomic block, cardiovascular depression and histamine release produced by polymyxin B in the cat. *Can. Anaesth. Soc. J.*, **26**, 196.

Lee, C., de Silva, A. J. C., and Katz, R. L. (1978). Antagonism of polymyxin B-induced neuromuscular and cardiovascular depression by 4-aminopyridine in the anesthetized cat. *Anesthesiology*, **49**, 256.

McLeod, K., Watson, M. J., and Rawlins, M. D. (1976). Pharmacokinetics of pancuronium in patients with normal and impaired renal function. *Br. J. Anaesth.*, **48**, 341.

McNall, P. G., Wolfson, B., Tuazon, J. G., and Siker, E. S. (1969). Use of pyridostigmine for the reversal of neuromuscular blockade. *Anesth. Analg. (Cleve.)*, **48**, 1026.

Matteo, R. S., Pua, E. K., Khambatta, H. J., and Spector S. (1977). Cerebrospinal fluid levels of d-tubocurarine in man. *Anesthesiology*, **46**, 396.

—— Spector, S., and Horowitz, P. E. (1974). Relation of serum d-tubocurarine concentration to neuromuscular blockade in man. *Anesthesiology*, **41**, 440.

Miller, R. D. (1976). Antagonism of neuromuscular blockade. *Anesthesiology*, **44**, 318.

—— Agoston, S., Booij, L. H. D. J., Kersten, U. W., Crul, J. F., and Ham, J. (1978). The comparative potency and pharmacokinetics of pancuronium and its metabolites in anesthetized man. *J. Pharmacol. Exp. Ther.*, **207**, 539.

—— —— van der Pol, F., Booij, L. H. D. J., Crul, J. F., and Ham, J. (1978). Hypothermia and the pharmacokinetics and pharmacodynamics of pancuronium in the cat. *J. Pharmacol. Exp. Ther.*, **207**, 532.

—— Booij, L. H. D. J., Agoston, S., and Crul, J. F. (1979). 4-Aminopyridine potentiates neostigmine and pyridostigmine in man. *Anesthesiology*, **50**, 416.

—— Matteo, R. S., Benet, L. Z., and Sohn, Y. J. (1977). The pharmacokinetics of d-tubocurarine in man with and without renal failure. *J. Pharmacol. Exp. Ther.*, **202**, 1.

—— Sohn, Y. J., and Matteo, R. S. (1976). Enhancement of d-tubocurarine neuromuscular blockade by diuretics in man. *Anesthesiology*, **45**, 442.

Morgan, K. G., and Bryant, S. D. (1977). The mechanism of action of dantrolene sodium. *J. Pharmacol. Exp. Ther.*, **201**, 138.

Munson, E. S., and Wagman, I. H. (1973). Elevation of lidocaine seizure threshold by gallamine: in rhesus monkeys. *Arch. Neurol.*, **28**, 329.

Nott, M. W., and Bowman, W. C. (1974). Actions of dantrolene sodium on contractions of the tibialis anterior and soleus muscles of cats under chloralose anaesthesia. *Clin. Exp. Pharmacol. Physiol.*, **1**, 113.

Owens, W. D., Waldbaum, L. S., and Stephen, C. R. (1978). Cardiac dysrhythmia following reversal of neuromuscular blocking agents in geriatric patients. *Anesth. Analg. (Cleve.)*, **57**, 186.

Pittinger, C. B., and Adamson, R. (1972). Antibiotic blockade of neuromuscular function. *Ann. Rev. Pharmacol.*, **12**, 169.

—— Eryasa, Y., and Adamson, R. (1970). Antibiotic-induced paralysis. *Anesth. Analg. (Cleve.)*, **49**, 487.

Proakis, A. G., and Harris, G. B. (1978). Comparative penetration of glycopyrrolate and atropine across the blood–brain and placental barriers in anesthetized dogs. *Anesthesiology*, **48**, 339.

Ramamurthy, S., Ylagan, L. B., and Winnie, A. P. (1971). Glyopyrrolate as a substitute for atropine: a preliminary report. *Anesth. Analg. (Cleve.)*, **59**, 732.

Savarese, J. J. (1979). The autonomic margins of safety of metocurine and d-tubocurarine in the cat. *Anesthesiology*, **50**, 40.

—— Ali, H. H., and Antonio, R. P. (1977). The clinical pharmacology of metocurine: dimethyltubocurarine revisited. *Anesthesioolgy*, **47**, 277.

—— —— Murphy, J. D., Padget, C., Lee, C., and Ponitz, J. (1975). Train-of-four nerve stimulation in the management of prolonged neuromuscular blockade following succinylcholine. *Anesthesiology*, **42**, 106.

—— Ginsburg, S., Lee, C., and Kitz, R. J. (1973). The pharmacology of new short-acting non-depolarizing ester neuromuscular blocking agents: clinical implications. *Anesth. Analg. (Cleve.)*, **56**, 982.

Somogyi, A. A., Shanks, C. A., and Triggs, E. J. (1976). Clinical pharmacokinetics of pancuronium bromide. *Eur. J. Clin. Pharmacol.*, **10**, 367.

—— —— —— (1977). Disposition kinetics of pancuronium bromide in patients with total biliary obstruction. *Br. J. Anaesth.*, **49**, 1103.

Standaert, F. G. (1964). The mechanisms of post-tetanic potentiation in cat soleus and gastrocnemius muscles. *J. Gen. Physiol.*, **47**, 987.

Stoyanov, E., Volchev, P., Shturbova, M., and Marinova, M. (1976). Clinical electromyomechanographic and electromyographic studies in decurarization with pymadine. *Anaesth. Resusc. Intens. Ther.*, **4**, 139.

Tseuda, K., Warren, J. E., McCafferty, L. A., and Nagle, J. P. (1978). Pancuronium bromide requirement during anesthesia for the morbidly obese. *Anesthesiology*, **48**, 438.

Waterman, P. M., and Smith, R. B. (1977). Tobramycin–curare interaction. *Anesth. Analg. (Cleve.)*, **56**, 587.

Waud, B. E., and Waud, D. R. (1972). The margin of safety of neuromuscular transmission in the muscle of the diaphragm. *Anesthesiology*, **37**, 417.

Waud, D. R., and Waud, B. E. (1975). Depolarization block and phase II block at the neuromuscular junction. *Anesthesiology*, **42**, 10.

Wright, J. M., and Collier, B. (1976). The site of neuromuscular block produced by polymixin B and rolitetracycline. *Can. J. Physiol. Pharmacol.*, **54**, 926.

—— —— (1977). The effects of neomycin upon transmitter release and action. *J. Pharmacol. Exp. Ther.*, **200**, 576.

Wyant, G. M., and Kao, E. (1974). Glycopyrrolate methobromide. I: Effect on salivary secretion. *Can. Anaesth. Soc. J.*, **21**, 230.

Br. J. Anaesth. (1980), **52**, 189

MINIMUM ARTIFICIAL LUNG EXPANSION NECESSARY FOR RESUSCITATION OF THE NEWBORN LAMB

R. S. VAUGHAN, W. W. MAPLESON, M. ROSEN AND K. M. LAURENCE

SUMMARY

In a group of seven lambs, pressure–volume relationships were obtained for the initial artificial expansion of the lungs in the intact chest and subsequent re-expansion after the lungs had been excised and collapsed. In a second group, of 12 severely asphyxiated lambs, the lungs were expanded in steps and circulatory resuscitation was achieved at pressures ranging from 1.75 to 3.5 kPa, geometric mean 2.3 kPa, with estimated corresponding volumes of 3–24 ml kg^{-1}, geometric mean 5.8 ml kg^{-1}. In a third group, of 24 severely asphyxiated lambs (mean pH 6.84), 22 were successfully resuscitated in the same manner and nine of these survived in apparent good health for more than 6 months. Any resuscitation regime for human neonates should take account of the finding that resuscitation occurred at pressures less than those necessary for full expansion and that, after the first sign of an increase in heart rate, there was a delay of 17–45 s before full circulatory improvement and of 3 min before full improvement in Pa_{O}.

In the newborn, artificial expansion can lead to rupture of the lung, since sufficient pressure has to be applied to open some lung units while others are close to their peak volume (Radford, 1960; Strang, 1977). In a study of 100 excised lungs from human infants (Rosen, Laurence and Mapleson, 1973) it was shown that no method could be devised whereby full expansion would always be achieved without some risk of lung rupture. However, it was suggested that partial expansion might be adequate for resuscitation. This is supported by Strang's finding (1977) that, in spontaneous expansion, not more than 30% of the functional residual capacity is established by the first breath. The present investigations in lambs were undertaken to determine the minimum degree of lung expansion required to resuscitate the animals.

METHOD

Experiments were carried out on three groups of fetal lambs of Welsh-bred ewes. In one group, the pressure–volume relationship of the initial expansion of the lamb's lungs was determined with the chest intact. Afterwards the lungs were excised and collapsed, and the pressure–volume relationship of re-expansion was determined. In a second group, the minimum applied pressure needed to effect circulatory improvement after severe asphyxiation was determined. Again, the lungs were excised and collapsed, and the pressure–volume relationship of their re-expansion was determined. In a third group, a similar asphyxiation and resuscitation procedure was used, but long-term survival was studied.

Pressure–volume relationships of the lamb lung (group A)

Seven ewes, pregnant with a mature singleton lamb (140 days+), were delivered by Caesarean section under caudal extradural block using 8–10 ml of 1% lignocaine and 1 in 200 000 adrenaline. After injection of pancuronium 0.5 mg and morphine 5 mg into the umbilical vein to prevent any respiratory effort, a cannula was inserted through a tracheostomy, the umbilical cord was clamped and the lambs (2.5–5 kg) were delivered. Using the apparatus of Rosen, Laurence and Mapleson (1973), the lungs were expanded in the intact chest using 5-ml increments of nitrogen and the pressures were noted. Nitrogen was used instead of air or oxygen to minimize gaseous uptake. The lambs were then sacrificed. The lungs were excised, fully collapsed and then re-expanded with 5-ml increments of air. During this procedure the "observed filling volume" (the volume at which the lungs appeared fully expanded) was noted.

R. S. VAUGHAN, M.B., B.S., F.F.A.R.C.S., D.A.; M. ROSEN, M.B., CH.B., F.F.A.R.C.S.; Department of Anaesthetics, University Hospital of Wales, Heath Park, Cardiff, CF4 4XW. W. W. MAPLESON, D.SC., F.INST.P., Department of Anaesthetics, Welsh National School of Medicine, Heath Park, Cardiff, CF4 4XN. K. M. LAURENCE, D.SC., F.R.C.P., F.R.C.PATH., Department of Child Health, Welsh National School of Medicine, Heath Park, Cardiff, CF4 4XN.

Correspondence to: M. R.

0007–0912/80/020189–07 $01.00

© Macmillan Journals Ltd 1980

Minimum applied pressure required for circulatory resuscitation (group B)

Twelve mature lambs (2.2–5.0 kg) were partly delivered under caudal- anaesthesia, the umbilical vein and the carotid and femoral arteries were cannulated, and the arterial pressure was recorded continuously. The lamb's neck was delivered through a separate uterine incision, ensuring that the mouth remained in the uterus. A tight-fitting metal cannula (3 cm in length) was introduced through a tracheostomy, closed off by a gas-tight tap and secured firmly. Airway pressure was recorded continuously from the proximal end of the tracheostomy tube. Pancuronium 0.5 mg and morphine 5 mg were then given i.v. to prevent any post-delivery respiratory effort.

Three minutes later the umbilical cord was clamped and the lamb delivered on to a heated table underneath an infra-red heater adjusted manually to maintain constant body temperature (±1.0 °C). An electric thermometer was inserted into the rectum.

Resuscitation was attempted when the systolic pressure or the heart rate had decreased by 20% of the measurements obtained before the umbilical cord was clamped. In an attempt to obtain volume data directly during resuscitation the lungs were expanded slowly, using the apparatus of Rosen, Laurence and Mapleson (1973) as in the group A lambs, with increments of 2–4 ml of oxygen. Once the heart rate began to increase the pressure was released and the lungs were ventilated by applying intermittently the greatest pressure recorded previously. This was done with a T-piece arrangement in series with a wide-bore water-blow-off valve and a continuous flow of oxygen. The pressure was increased only if the arterial pressure or heart rate subsequently decreased (this occurred in one lamb only). When resuscitation (defined as a pronounced increase in heart rate and arterial pressure to steady values) had been clearly established for some minutes, circulatory arrest was induced by potassium chloride 13 mmol i.v.

Pa_{O_2} and pH were measured in samples of arterial blood from the carotid artery taken just before delivery, at cord clamping, 30 s after cord clamping, and at intervals during the resuscitation procedure. Haemoglobin and packed cell volume were measured initially (means 13.4 g dl^{-1} and 42%) and just before the animal was sacrificed (means 11.6 g dl^{-1} and 38%). In eight lambs the lungs were excised, fully collapsed and re-expanded as in the group A lambs.

Survival after resuscitation (group C)

Twenty-four mature lambs (2–4.5 kg) were partly delivered under caudal extradural anaesthesia. The trachea was intubated directly with a 3.0-mm cuffed endotracheal tube, the cuff being over-inflated to ensure an airtight seal. The airway was connected in an airtight manner to a manometer so that airway pressure could be measured but no air or oxygen could be drawn into the lungs. The arterial pressure was monitored through a catheter placed in the umbilical artery. The lambs were delivered and the umbilical cord was immediately clamped, but resuscitation was delayed until after the last respiratory effort (the "last gasp") and until the systolic arterial pressure or heart rate had decreased by 20% from the value just before cord-clamping. The lungs were expanded in the same manner as in group B, using oxygen in 18 lambs and air in six lambs, until heart rate and systolic pressure began to increase. The lungs were then ventilated at the greatest pressure used until each was "resuscitated" (as defined above) and subsequently breathed, or until death occurred. If cardiac arrest occurred, external cardiac massage was applied while the lung expansion procedure was continued. Sodium bicarbonate 1 mol litre^{-1}, 5–20 ml was administered to those eight lambs whose conjunctival reflex responses did not return after resuscitation. Umbilical arterial blood samples were taken at delivery, cord clamping, resuscitation and sporadically afterwards.

RESULTS

Pressure–volume relationships (group A)

Figure 1 shows the mean pressure–volume curves for the seven lambs in group A (not resuscitated) for the circumstances indicated. Volumes are expressed in ml kg^{-1} to reduce the scatter between the lambs and the standard errors of the means.

Minimum pressure and volume required for circulatory resuscitation (group B)

For the 12 lambs in group B the cumulated per cent resuscitated is plotted against pressure at resuscitation and against the estimated corresponding volume in ml kg^{-1} (fig. 2).

By expanding the lungs with known increments it was hoped to obtain the volume required for resuscitation directly but, in practice, it was impossible to determine the actual expansion because of the effect of simultaneous gas uptake. Therefore it was necessary to estimate the volume requirement indirectly. This was done in two different ways. In

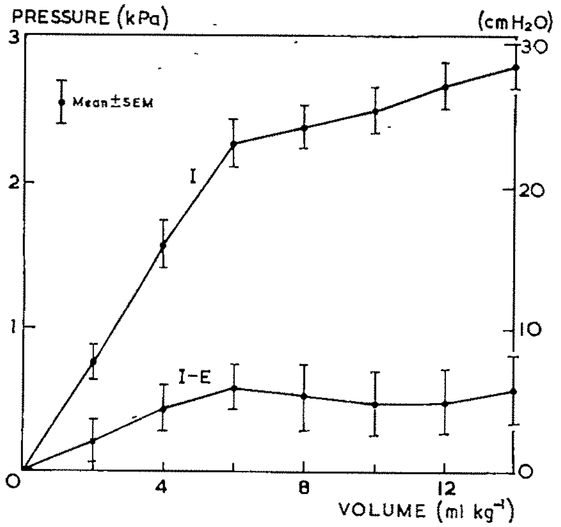


FIG. 1. Mean pressure–volume curves for seven lambs in group A: (I) initial expansion in the intact chest with nitrogen and with circulation present; (I – E) excess of the pressures in (I) over those obtained during subsequent re-expansion after sacrifice, and excision and collapse of the lungs. (For each lamb, pressures at volume intervals of 2 ml kg^{-1} were obtained by linear interpolation between the pressures observed after each volume increment, all of which were 5 ml irrespective of body mass.)

eight ambs pressure–volume curves were obtained during re-expansion of the lungs after excision and collapse; these curves were each corrected by, at each volume, adding to the observed pressure the corresponding mean pressure difference between intact and subsequent excised expansions of the lungs of the group A lambs (read from curve I – E in fig. 1). Volumes corresponding to the resuscitation pressures were then read from the resulting corrected curves. In the remaining four group B lambs no individual pressure–volume curves were obtained; therefore, volumes corresponding to the resuscitation pressures were read from the mean pressure–volume curve for the intact-chest expansions in group A (curve I in fig. 1).

Resuscitation pressures ranged from 1.75 to 3.5 kPa, geometric mean 2.3 kPa, and estimated resuscitation volumes from 3 to 24 ml kg^{-1}, geometric mean 5.8 ml kg^{-1}. The greatest arterial oxygen tensions recorded after resuscitation ranged from 7.9 to 24.9 kPa, mean 15.8. The mean pH of carotid artery blood was 7.12 (SD 0.14) at cord clamping and less than 6.89 (SD > 0.12) at the first signs of resuscitation. (Readings for some lambs were less than the minimum recordable (6.80) on the pH meter used at that time.)

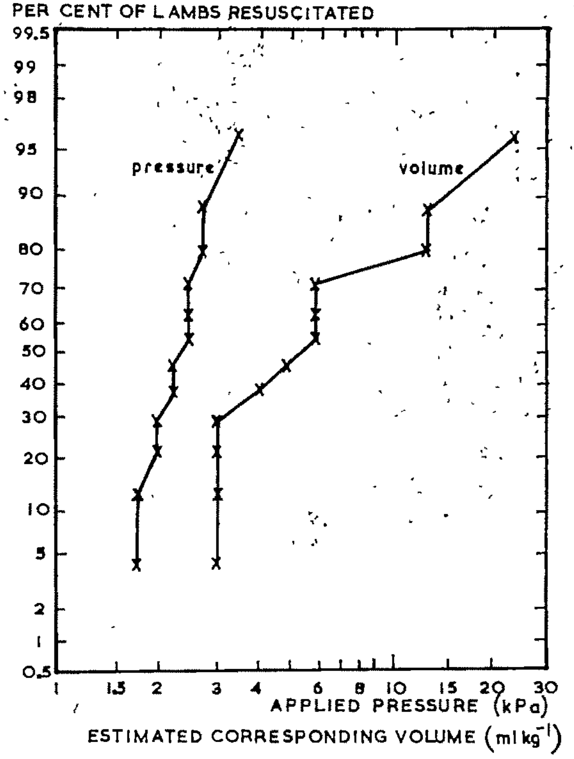


FIG. 2. Percentage of 12 lambs in group B which were resuscitated by the pressures (and the estimated corresponding volumes—see text) on the abscissa.

Survival after resuscitation (group C)

Five of the 24 lambs in group C suffered cardiac arrest; three of them were resuscitated, but in the other two circulation could not be re-established. Circulatory resuscitation was achieved in 22 lambs and 21 of these breathed spontaneously. Of these 21, 11 survived for more than 24 h. One of these 11 died at 26 h and one at 4 days but nine (three of which had received sodium bicarbonate) were still alive and apparently normal at least 6 months later. Of the 12 lambs which were resuscitated and breathed spontaneously but survived 4 days or less, 10 died of respiratory or circulatory failure and two had obvious neurological damage and were destroyed. Three (50%) of the six resuscitated with air survived more than 24 h, as did eight (44%) of the 18 resuscitated with oxygen. In no animal was there macroscopic evidence of traumatic lung damage.

In seven animals resuscitated with oxygen, serial umbilical arterial samples were taken regularly after the first sign of an increase in heart rate. Figure 3 shows that arterial Po_2 increased continuously for about 3 min even though the intermittent positive pressure used for ventilation during this time was kept constant at the value which produced resuscitation.

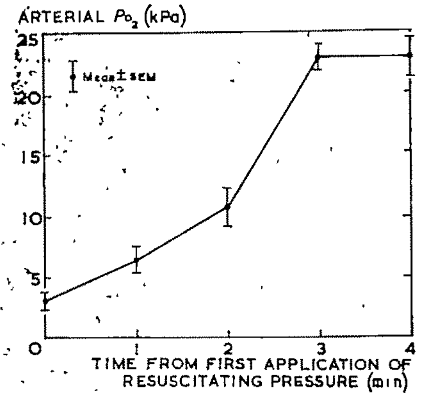


FIG. 3. Arterial P_{O_2} during intermittent positive pressure ventilation at a pressure equal to that (1.75–2.75 kPa) which produced resuscitation; means for seven of the group C lambs resuscitated with oxygen.

The timing of the other events was as follows: cord clamping to the start of the resuscitation procedure = 1–10 min (mean 5.1 min); first sign of heart rate increase to full "resuscitation" (recorded in 10 animals) = 17–45 s (mean 26 s); start of the resuscitation procedure to the first gasp (measured in 21 animals) = 1–32 min (mean 8.4 min); start of the resuscitation procedure to fully established spontaneous respiration = 1–70 min (mean 16.5 min).

The pressures required for resuscitation ranged from 2.3 to 3.0 kPa, geometric mean 2.6 kPa. The mean pH of umbilical artery blood was 7.19 (SD 0.16) at cord clamping and 6.84 (SD 0.10) at the first sign of resuscitation.

DISCUSSION

Pressure–volume curves

The pressure–volume curves for the lamb broadly resemble those for man (Rosen, Laurence and Mapleson, 1973) in that they comprise an opening phase (steep increase in pressure for little increase in volume) followed by a filling phase (little increase in pressure for large increases in volume). However, the subsequent hyperdistension phase (renewed steep increase in pressure) found in man was generally absent in the lamb. In addition, the "spikes" of pressure often encountered at small volumes in man (Rosen, Laurence and Mapleson, 1973) were absent in the lamb even when, in some preliminary studies, initial expansions were made in excised lungs. The "observed filling volume" (the volume at which the lungs appeared to be just fully expanded) was more difficult to identify than in man. Perhaps these various differences are attributable, at least in part, to the way in which the human lung tends to expand lobe by lobe whereas, in the lamb, all the lobes tend to expand together. Whatever the cause, the observed filling volumes were considered unreliable in detail and, because of the absence of a hyperdistension phase, the algorithm (Rosen, Laurence and Mapleson, 1973) for a "calculated filling volume" could not be used. Accordingly, all volumes are expressed, not as a percentage of the observed filling volume, but in ml per kg body mass of the lamb. Nevertheless, it is worth recording that, in 25 lambs, including some from preliminary studies, the filling volumes as assessed by the same observer as in Rosen, Laurence and Mapleson (1973) ranged from 6 to 32 ml kg^{-1} (mean 17 ml kg^{-1}).

Like Milner and Saunders (1977), in their study of the spontaneous expansion of human neonatal lungs, we found little evidence of an "opening pressure", which in our expansion procedure would be reflected by a large pressure produced by even the smallest volume increment. Indeed, in our artificial expansions, the initial rate of increase of pressure with increasing volume was generally even slower than in Milner and Saunders' spontaneous expansions; but they made recordings during natural inspiration, so that their oesophageal pressure measurements included the pressure decrease across the airways as a result of inspiratory flow, whereas our pressure measurements were all made at zero flow.

Pressure and volume required for resuscitation

Since figure 2 is plotted with probability and logarithmic axes, the closeness to a straight line of the plot of cumulated per cent resuscitated *v.* applied pressure indicates that the resuscitation pressures were nearly log-normally distributed. Extrapolation suggests that only 2% of lambs would be resuscitated by a pressure of 1.5 kPa.

The maximum oesophageal pressure changes observed by Milner and Saunders (1977) in the first breaths of human neonates are not strictly comparable, since they included the pressure decrease across the chest wall. However, they were of the same order of magnitude, ranging from 0.5 to 3.8 kPa in 13 infants, compared with our 1.75 to 3.5 kPa in 12 lambs.

The estimated resuscitation volumes do not conform as closely as the resuscitation pressures to a log-normal distribution, and the less-steep line indicates a larger relative standard deviation. This may be a genuine finding but, since the estimates of resuscitation volume are indirect, and especially since four of them, including the two greatest, had to be derived from the mean "intact" pressure–volume curve, the highest by extrapolation, the finding may be spurious. Even so, taking the estimates of resuscitation volume as they are, their mean (geometric mean because of the near log-normal distribution) is only 6 ml kg^{-1}, or only about one-third of the mean observed filling volume and one-fifth of the functional residual capacity (30 ml kg^{-1}) of 11 newborn lambs (gestational age 138 days +) studied by Shaffer and colleagues (1976). In the human neonate 6 ml kg^{-1} is only one-quarter of the mean observed filling volume (Rosen, Laurence and Mapleson, 1973) and one-fifth of the functional residual capacity (Nelson, 1966). Thus the supposition of Rosen and his associates that resuscitation could be achieved by expanding to much less than the observed filling volume is well supported.

The volumes observed by Milner and Saunders in the first spontaneous inspiration of human neonates, 13–90 ml or, say, 4–28 ml kg^{-1}, were very similar to our range of 3–24 ml kg^{-1} in lambs.

Survival after resuscitation

It is important to note that from the first sign of an increase in heart rate there was a delay (probably because of reduced cardiac output) of 17–45 s before full circulatory resuscitation, and of nearly 3 min before the full increase in Pa_{O_2} occurred (fig. 3). Therefore, if the human neonate behaves similarly it would be particularly important in clinical practice to monitor heart rate continuously to avoid unnecessary expansion and possible consequent rupture of some lungs.

The present results for survival can be compared with those from a study of Dawes and others (1963) who examined the effects of alkali on survival. In their study the lungs of 19 asphyxiated mature lambs were expanded with room air at unspecified pressure and volume from a Starling pump. Table I shows that our resuscitation and survival rates were better than those of Dawes and others, significantly so ($P < 0.02$) in terms of survival for 48 h or more. There were differences between the two studies: we resuscitated most of our lambs with oxygen, but obtained a similar success rate in the six resuscitated with air; we asphyxiated our lambs to a specified degree of cardiovascular depression rather than for a specified time, but at the first signs of resuscitation our lambs were more acidotic—mean pH 6.84 compared with means, in the work of Dawes and others, of 7.00 in 10 untreated lambs and greater than 7.3 in nine which received an infusion of sodium carbonate in glucose solution during the asphyxia. Therefore it seems that our resuscitation procedure was more effective.

TABLE I. *Survival of lambs after asphyxiation and ventilatory resuscitation. * By χ^2 test with Yates' correction*

	Dawes and others (1963)		Present study		P* for difference between studies
	No.	(%)	No.	(%)	
Total	19	(100)	24	(100)	—
Resuscitated	15	(79)	22	(92)	n.s.
Survived ⩾24 h	7	(37)	11	(46)	n.s.
Survived ⩾48 h	1	(5)	10	(42)	< 0.02

If a similar pattern of treatment were applied to human neonates it is likely that, as in lambs, it would be more successful than the method of Dawes and others (1963). However, apart from general uncertainty arising from unknown inter-species differences, it is likely to be less successful than in lambs: because of the "spikes" on some human pressure–volume curves, unusually great resuscitation pressures may be required in some babies and this may lead to an increased risk of lung rupture and to delay in achieving adequate expansion. On the other hand, if resuscitation were by the application of known pressures, increasing according to a "staircase" as recommended by Rosen, Laurence and Mapleson (1973), it is likely that it would be more rapid than the volume method used here and, therefore, possibly more successful.

In our lambs nine of 24 (38%) survived for more than 6 months; two others had to be destroyed because of serious neurological abnormalities. Therefore, even an optimum "pressure staircase" pattern of treatment, applied to severely hypoxic human neonates, cannot be expected to yield a survival rate better than about one-half, and some survivors are likely to be left with neurological damage.

CONCLUSIONS

(1) Severely hypoxic fetal lambs can be resuscitated with approximately one-quarter lung expansion and certainly with less than full expansion.

(2) The pressures required to expand the lungs just sufficiently for resuscitation ranged from 1.75 to 3.5 kPa.

(3) These resuscitation pressures and volumes did not cause rupture or macroscopic lung damage.

(4) It is essential to watch carefully for the first sign of circulatory improvement in order to avoid excessive pressure in the lung because full circulatory resuscitation may not occur until some tens of seconds later.

(5) Expanding the lungs with 100% oxygen or air made no difference to the percentage of animals that ultimately survived, but the number of experiments was small and more would be required to determine the optimum oxygen concentration for resuscitation.

(6) If the response of human neonates is not greatly different from that of lambs, prompt application of an optimum pressure-staircase technique might well resuscitate about 50% of all severely hypoxic babies, although there might still be some survivors who would suffer from neurological defects.

(7) Studies in a range of other species might be desirable to shed light on the optimum size and frequency of pressure steps.

ACKNOWLEDGEMENTS

We thank the staff at the Leonard West Research Laboratory at Sully Hospital, South Glamorgan, for their skilful help. The project was supported by a grant from the Welsh Office.

REFERENCES

Dawes, G. S., Jacobson, H. N., Mott, J. C., Shelley, H. J., and Stafford, A. (1963). The treatment of asphyxiated, mature foetal lambs and rhesus monkeys with intravenous glucose and sodium carbonate. *J. Physiol. (Lond.)*, **169**, 167.

Milner, A. D., and Saunders, R. A. (1977). Pressure and volume changes during the first breath of human neonates. *Arch. Dis. Child.*, **52**, 918.

Nelson, N. M. (1966). Neonatal pulmonary function. *Pediatr. Clin. N. Am.*, **13**, 769.

Radford, E. P. jr. (1960). Mechanical factors determining alveolar configuration. *Am. Rev. Respir. Dis.*, **81**, 743.

Rosen, M., Laurence, K. M., and Mapleson, W. W. (1973). Artificial expansion of the newborn human lung. *Br. J. Anaesth.*, **45**, 535.

Shaffer, T. H., Delivoria-Papadopoulos, M., Arcinue, E., Paez, P., and Dubois, A. B. (1976). Pulmonary function in premature lambs during the first few hours of life. *Respir. Physiol.*, **28**, 179.

Strang, L. B. (1977). *Neonatal Respiration*, p. 66. Oxford: Blackwell Scientific Publications.

EXPANSION ARTIFICIELLE MINIMALE DES POUMONS NECESSAIRE POUR LA REANIMATION D'UN AGNEAU NOUVEAU-NE

RESUME

On a déterminé sur un groupe de sept agneaux, les relations pression–volume nécessaires pour obtenir l'expansion artificielle initiale des poumons dans la poitrine intacte et la réexpansion qui lui fait suite après que les poumons aient été excisés et collabés. Sur un second groupe de 12 agneaux souffrant d'une asphyxie prononcée, les poumons ont été gonflés par degrés et on est arrivé à une réanimation circulatoire allant de 1,75 à 3,5 kPa, moyenne géométrique 2,3 kPa, avec volumes correspondants estimés de 3–24 ml kg^{-1}, moyenne géométrique de 5,8 mk kg^{-1}. Sur un troisième groupe de 24 agneaux sérieusement asphyxiés (pH moyen 6,84) 22 ont été réanimés avec succès de la même manière et neuf d'entre eux ont survécu en bonne santé apparente pendant plus de 6 mois. Tout régime de réanimation pour les nouveaux-nés humains doit tenir compte de ces résultats à savoir que la réanimation se produit à des pressions inférieures à celles nécessaires pour le pleine expansion des poumons et qu'après le premier signe d'une augmentation de la fréquence cardiaque, il s'écoule un délai de 17–45 s et même davantage avant qu'il y ait une amélioration circulatoire totale, et de 3 min avant une amélioration complète de la Pa_{O_2}.

MINIMALE KÜNSTLICHE LUNGENEXPANSION, DIE FÜR WIEDERBELEBUNG NEUGEBORENER LÄMMER NÖTIG IST

ZUSAMMENFASSUNG

Bei einer Gruppe von sieben Lämmern wurden Druck-Volumsverhältnisse für die anfängliche künstliche Lungenexpansion in dem intakten Brustraum, und für die folgende Wiederexpansion nach Entnahme und Kollabierung der Lungen ausfindig gemacht. In einer zweiten Gruppe von 12 schwer asphyktischen Lämmern wurden die Lungen stufenweise expandiert, und Kreislaufwiederbelebung wurde bei Druckbereichen von 1,75 bis 3,5 kPa—einem geometrischen Mittel von 2,3 kPa—erzielt, bei geschätzten, entsprechenden Volumen von 3–24 ml kg^{-1}. In einer dritten Gruppe schwer asphyktischer Lämmer (mittleres pH 6,84) wurden 22 erfolgreich wiederbelebt auf dieselbe Weise, und neun davon überlebten in anscheinend gutem Zustand auf 6 Monate. Alle Wiederbelebungsmassnahmen für menschliche Neugeborene sollten berücksichtigen, dass die Wiederbelebung hier bei Drücken stattfand, die unter denen für vollständige Expansion notwendigen lagen, und dass nach den ersten Anzeichen einer erhöhten Pulszahl eine Verzögerung von 17–45 s. und mehr eintrat, ehe eine volle Kreislaufwiederherstellung eintrat, und eine Verzögerung von 3 min, ehe eine vollständige Verbesserung von Pa_{O_2} stattfand.

EXPANSION PULMONAR ARTIFICIAL MINIMA NECESARIA PARA LA RESUCITACION DEL CORDERO

SUMARIO

Se obtuvieron en un grupo de siete corderos las relaciones presión–volumen para la expansión artificial inicial de los pulmones de un tórax intacto y re-expansión consecutiva después de la extirpación y del colapso de los pulmones. En un segundo grupo de 12 corderos severamente asfixiados, se expandieron los pulmones en varias etapas y se consiguió la resucitación circulatoria a presiones que variaban entre 1.75 y 3.5 kPa, media geométrica de 2,3 kPa, con volumenes correspondientes estimados de 3–24 ml kg^{-1}, media geométrica de 5,8 ml kg^{-1}. En un tercer grupo de 24 corderos severamente asfixiados (pH medio de 6,84), se resucitaron con éxito a 22 de ellos de la misma manera y nueve de los mismos sobrevivieron en buena salud aparente durante más de 6 meses. Cualquier regimen de resucitación para neonatos humanos debe tener en cuenta el hecho de que la resucitación ocurrió en presiones más bajas que las que se necesitan para la plena expansión y que, después de la primera señal de un aumento del ritmo cárdiaco, hubo una demora de 17–45 s y más aún antes de la mejoría total de la circulación y de 3 min antes de la mejoría total del Pa_{O_2}.

Br. J. Anaesth. (1980), **52**, 197

EFFECT OF ACUTE HYPOCAPNIA ON RENAL FUNCTION IN THE DOG ARTIFICIALLY VENTILATED WITH NITROUS OXIDE, OXYGEN AND HALOTHANE

J. M. HUNTER, R. S. JONES AND J. E. UTTING

SUMMARY

Changes from normocapnia to hypocapnia (and *vice versa*) were induced in dogs lightly anaesthetized with nitrous oxide and halothane and subjected to passive pulmonary ventilation. During hypocapnia estimated renal plasma flow and urine production were greater than in normocapnia, and renal vascular resistance was decreased greatly compared with normocapnia. There was little change in glomerular filtration rate.

In a previous study (Hunter et al., 1979), we presented those alterations in renal function which took place when changes from normocapnia to hypocapnia (and *vice versa*) were induced in dogs lightly anaesthetized with nitrous oxide and fentanyl and subjected to passive pulmonary ventilation. It was found that, during hypocapnia, estimated renal plasma flow (ERPF) was twice that during normocapnia and that glomerular filtration rate (GRF) and urine output (V) were increased in approximately similar proportions while renal vascular resistance (RVR) was halved.

As this was a finding of some importance, we repeated the experiments, using an identical experimental plan, but administering a low concentration of halothane as the adjuvant to nitrous oxide instead of a small dose of fentanyl.

METHODS

Twelve experiments were conducted on eight healthy mature labrador dogs weighing 18–31 kg. In half the experiments Pa_{CO_2} was maintained first at near physiological values and hypocapnia was induced later. In the other half, the order was reversed. The period of study at each value of Pa_{CO_2} was 90 min.

The experiments differed from those described previously (Hunter et al., 1979) only in the technique of anaesthesia. In the previous study anaesthesia was induced with thiopentone and fentanyl and maintained with a mixture of nitrous oxide in oxygen and fentanyl 0.4 μg min^{-1}. Alcuronium was administered to produce neuromuscular blockade. The only difference in this study was that no fentanyl was given, either at induction or for the maintenance of anaesthesia, and that halothane was used as the adjuvant throughout the anaesthetic (at inspired concentration 0.4–0.5%), using a Dräger Vapor vaporizer calibrated using a mass spectrometer.

RESULTS

Acid–base state

Mean Pa_{CO_2} during what is described as normocapnia was 5.4 kPa, range 4.3–6.5 kPa; during hypocapnia the mean was 2.6 kPa, range 1.4–3.6 kPa; the corresponding mean arterial pH was 7.31, range 7.13–7.54 and 7.55, range 7.34–7.78, respectively. Using values for pK′ and solubility of carbon dioxide obtained from human blood the mean actual bicarbonate concentration was 20.0 mmol litre^{-1} in normocapnia and 16.3 mmol litre^{-1} during hypocapnia. The difference between the bicarbonate values was statistically significant ($P < 0.01$).

Indices of renal function

There was a decrease in renal vascular resistance during hypocapnia ($P < 0.01$, paired t test) (table I). Estimated renal plasma flow increased during hypocapnia ($P < 0.05$), as did urine output ($P < 0.05$). There was no difference between the glomerular filtration rate in normocapnia and that in hypocapnia.

The arterial pressure was significantly lower in hypocapnia than in normocapnia ($P < 0.01$).

DISCUSSION

During hypocapnia, we found a marked decrease in renal vascular resistance and an increase in estimated

---

J. M. HUNTER, M.B., CH.B., F.F.A.R.C.S.; R. S. JONES, M.V.SC. M.R.C.V.S., D.V.A.; J. E. UTTING, M.A., M.B., F.F.A.R.C.S.; University Department of Anaesthesia, Royal Liverpool Hospital, P.O. Box 147, Liverpool, L69 3BX.

0007-0912/80/020197-02 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Mean values for estimated renal plasma flow (ERPF), glomerular filtration rate (GFR), renal vascular resistance (RVR) (mm Hg ml^{-1} min^{-1} per* 100 *g kidney weight) urine volume (V) and mean arterial pressure (MAP) for dogs during normocapnia and hypocapnia. Note that hypocapnia preceded normocapnia in half the experiments and* vice versa

	ERPF (ml min^{-1} kg^{-1})	GFR (ml min^{-1} kg^{-1})	RVR	V (ml min^{-1})	MAP (mm Hg)
Normocapnia					
(Pa_{CO_2} 4.3–6.5 kPa)	24.1	10.2	0.31	2.0	118.0
SEM	7.7	2.2	0.07	0.3	4.0
SD	46.5	13.4	0.25	1.7	19.0
Hypocapnia					
(Pa_{CO_2} 1.4–3.6 kPa)	29.3	11.3	0.17	3.2	107.0
SEM	6.4	2.0	0.05	0.3	2.6
SD	38.6	12.0	0.16	2.0	15.6

renal plasma flow and urine production; glomerular filtration rate was little changed. Except for this last variable, which had been previously found to increase, these findings are similar to those of our previous study (Hunter et al., 1979). The only difference in the experimental conditions between the studies is that, in the present study, halothane replaced low dose fentanyl as an adjuvant to nitrous oxide. Indeed, using the unpaired *t* test, there were no statistically significant differences between the comparable variables in the two studies (for example, ERPF in normocapnia in the fentanyl series compared with ERPF in normocapnia in the halothane series).

This study confirms the finding that, in the lightly anaesthetized and paralysed dog, there is a considerable change in renal circulation and urine production during hypocapnia.

ACKNOWLEDGEMENTS

This work was funded by a grant from the Regional Research Committee of the Mersey Regional Health Authority. The authors wish to acknowledge their gratitude to Miss Christina Mann for technical assistance.

REFERENCE

Hunter, J. M., Jones, R. S., Lamplugh, G., and Utting, J. E. (1979). The effect of hypocapnia on some aspects of renal function in dogs. *Br. J. Anaesth.*, **51**, 725.

EFFET D'UNE HYPOCAPNIE AIGUE SUR LA FONCTION RENALE D'UN CHIEN VENTILE ARTIFICIELLEMENT A L'AIDE DE PROTOXYDE D'AZOTE, D'OXYGENE ET D'HALOTHANE

RESUME

On a provoqué sur des chiens légèrement anesthésiés à l'aide de protoxyde d'azote et d'halothane, et soumis à une ventilation pulmonaire passive, des variations allant de la normocapnie à l'hypocapnie (et *vice versa*). Pendant l'hypocapnie, la production d'urine et le débit de plasma rénal estimés ont été plus élevés que pendant la normocapnie, alors que la résistance vasculaire rénale a fortement diminué par rapport à la normocapnie. Il n'y a eu que très peu de variations dans le taux de filtration glomérulaire.

WIRKUNG AKUTER HYPOKAPNIE AUF DIE NIERENFUNKTION BEIM HUND, DER DURCH STICKOXYD, SAUERSTOFF UND HALOTHAN KÜNSTLICH BELÜFTET WIRD

ZUSAMMENFASSUNG

Wechsel von Normokapnie zu Hypokapnie (und *umgekehrt*) wurden bei leicht mit Stickoxyd und Halothan narkotisierten Hunden eingeleitet, die einer passiven Lungenbelüftung ausgesetzt waren. Während Hypokapnie waren der geschätzte Nierenplasmafluss und die Urinproduktion grösser als bei Normokapnie, und der Gefässwiderstand der Niere wurde stark verringert, verglichen mit Normokapnie. Die glomerulare Filtrierungsrate war kaum verändert.

EFECTO DE HIPOCAPNIA AGUDA EN LA FUNCION RENAL DEL PERRO ARTIFICIALMENTE VENTILADO CON OXIDO NITROSO, OXIGENO Y HALOTANO

SUMARIO

Se indujeron cambios desde normocapnia hasta hipocapnia (y *vice versa*) en perros ligeramente anestesiados con óxido nitroso y halotano y que fueron sometidos a una ventilación pulmonar pasiva. Durante la hipocapnia, el flujo estimado del plasma renal y la producción de orina fueron mayores que en la normocapnia y la resistencia vascular renal disminuyó mucho en comparación con la normocapnia. Hubo apenas algún cambio en el ritmo de filtración glomerular.

Br. J. Anaesth. (1980), **52**, 199

EFFECTS OF ANAESTHETICS ON GUINEAPIG TRACHEAL SMOOTH MUSCLE

F. OKUMURA AND M. A. DENBOROUGH

SUMMARY

The effects of i.v. and local anaesthetics on guineapig tracheal smooth muscle have been investigated *in vitro*. Diazepam, propanidid and ketamine induced relaxation and antagonized histamine-, acetylcholine- and potassium chloride-induced contractures in the tracheal smooth muscle. The relaxing effects of the anaesthetics were not affected by propranolol. Thiopentone, at concentrations which would be used clinically, caused contracture of the tracheal smooth muscle. Morphine induced relaxation and antagonized histamine-induced contracture, but did not antagonize acetylcholine- or potassium chloride-induced contractures. Lignocaine and procaine, at clinical concentrations, induced contracture of tracheal smooth muscle. Large doses of lignocaine relaxed the tracheal muscle, but large doses of procaine induced spontaneous rhythmical movements. Lignocaine and procaine antagonized contractures induced by histamine, acetylcholine and potassium chloride.

Anaesthetic drugs may affect airways smooth muscle, and may be implicated in the onset of bronchospasm, particularly in patients who suffer from asthma.

This has prompted the present investigation in which the effects of commonly used i.v. and local anaesthetics on guineapig tracheal muscle have been compared *in vitro*.

METHODS

The tracheal smooth muscle was prepared by a modification of the method described by Akcasu (1959). One hundred and four tracheal preparations were made from 34 adult guineapigs of both sexes.

Each guineapig was killed by stunning and bleeding, after which the trachea from the larynx to the carina was quickly removed and placed in a muscle buffer solution at 37 °C. After removing any attached tissue the trachea was cut transversely to leave a piece about 5 mm long (four cartilages long), and then cut longitudinally, leaving the tracheal smooth muscle intact. A metal ring was tied to each end of this preparation with cotton thread. One ring of the preparation was attached to a force transducer (FO202 SER, Watson Victor Ltd) via a thin stainless steel wire, the other to a fixed glass rod. The tracheal preparation was immersed in a 25-ml bath of buffer, bubbled with a mixture of 5% carbon dioxide in oxygen (carbogen) and maintained at 37 °C. The composition of the buffer (mmol litre^{-1}) was: NaCl 121.2, KCl 5.4, $MgSO_4$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 15.0, $CaCl_2$ 2.5 and glucose 11.5.

The isometric changes in tension of the tracheal preparations were recorded on a Perkin-Elmer Recorder 56 through a Sanei 6M51 Strain Amplifier. For examination of the direct effects of anaesthetics on the tracheal smooth muscle, the initial resting tension used in the muscle preparations was 2 g. The anaesthetics were added to the organ bath in cumulative doses. The results are expressed as a percentage relaxation or contracture in comparison with the amount of relaxation caused by isoprenaline 50 μmol litre^{-1}, which was found to induce maximal relaxation.

The antagonism between the anaesthetics and three bronchoconstrictors (histamine, acetylcholine and potassium chloride) was also studied. The contractures to histamine 10 μmol litre^{-1} (1.78 g $\pm$ 0.56 SD, $n = 5$), acetylcholine 10 μmol litre^{-1} (1.93 g $\pm$ 0.29 SD, $n = 7$) and potassium chloride 40 mmol litre^{-1} (1.91 g $\pm$ 0.93 SD, $n = 14$) were of similar size. After establishing an initial resting tension of 1.5 g, each bronchoconstrictor was added to the bath to produce the concentrations given above. As soon as the contracture plateau induced by the bronchoconstrictor had been reached, successive doses of the

---

F. OKUMURA,* M.D., PH.D.; M. A. DENBOROUGH, M.D., D.PHIL., D.SC., F.R.C.P., F.R.A.C.P.; Department of Clinical Science, John Curtin School of Medical Research, The Australian National University, Canberra, A.C.T. 2601, Australia.

* Present address: Department of Anesthesiology, National Cardiovascular Center, Fujishirodai Suita, Osaka, Japan 565.

0007-0912/80/020199-06 $01.00

© Macmillan Journals Ltd 1980

anaesthetic were added. The results are expressed as a percentage relaxation or contracture in comparison with the contracture induced by the bronchoconstrictor.

Each experiment used from four to 10 tracheal preparations. The results obtained with different drugs were reproducible. The standard deviations for the results from individual doses of different drugs were of the order of ±5–10 per cent. The drugs used were: thiopentone sodium (Pentothal); ketamine hydrochloride (Ketalar); morphine sulphate; propanidid (Epontol); diazepam (Valium); lignocaine hydrochloride; procaine hydrochloride; histamine dihydrochloride; acetylcholine chloride; isoprenaline hydrochloride (Isuprel); propranolol hydrochloride (Inderal). All drugs except propanidid, diazepam, isoprenaline and propranolol were dissolved in distilled water. Commercial preparations for injections were used in the case of these four drugs.

RESULTS

The direct effects of the anaesthetics on the intrinsic tone of guineapig tracheal muscle are shown in figure 1. Diazepam, propanidid, morphine and ketamine produced dose-dependent relaxation. Thiopentone caused contracture at concentrations less than 0.4 mmol litre^{-1}, but relaxation at concentrations greater than this.

Lignocaine induced large contractures, the maximal occurring at a concentration of 950 µmol litre^{-1}.

Procaine also produced contracture, and at concentrations greater than 1.4 mmol litre^{-1} the tracheal muscle preparation exhibited spontaneous rhythmical contraction and relaxation.

The effects of the anaesthetics on the contractures induced by histamine and acetylcholine are shown in figures 2 and 3. All the anaesthetics antagonized histamine-induced contracture (fig. 2) except for lignocaine at a concentration of less than 1.5 mmol litre^{-1}, and morphine sulphate at a concentration of less than 50 µmol litre^{-1}. Procaine produced relaxation of histamine-induced contracture, although procaine by itself caused contracture.

All the anaesthetics except morphine and ketamine (at a concentration less than 1.5 mmol litre^{-1}) reversed acetylcholine-induced contracture (fig. 3).

The effects of anaesthetics on contractile responses to potassium chloride are shown in figure 4. All anaesthetics except morphine and lignocaine (at concentrations less than 1.5 mmol litre^{-1}), antagonized potassium chloride-induced contractures.

Propranolol 13.5 µmol litre^{-1} completely blocked the effect of isoprenaline 50 µmol litre^{-1}, but had no effect on the relaxing ability of the anaesthetics tested (fig. 5). The concentrations of anaesthetics required to produce a 50% antagonism of the contractures induced by histamine 10 µmol litre^{-1}, acetylcholine 10 µmol litre^{-1} and potassium chloride 40 mmol litre^{-1} were obtained from figures 2, 3 and 4 (table I). Practical difficulties prevented the calculation of EC_{50} values for each of the anaesthetic drugs.

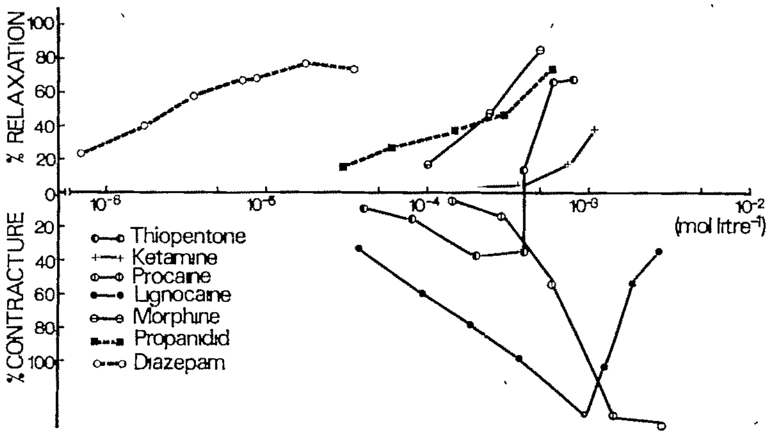


FIG. 1. The effects of anaesthetics on guineapig tracheal smooth muscle. The results are expressed as a percentage relaxation or contracture in comparison with the amount of relaxation induced by isoprenaline 50 µmol litre^{-1}. Per cent relaxation or contracture is shown on the vertical axis and the concentrations of the anaesthetic drugs are shown on the horizontal axis.

TABLE I. *Concentrations of anaesthetics required to produce 50% relaxation of the contractures induced in guineapig tracheal smooth muscle by histamine 10 μmol litre^{-1}, acetylcholine 10 μmol litre^{-1} and potassium chloride 40 mmol litre^{-1}*

Anaesthetic (mol litre^{-1})	Histamine (10 μmol litre^{-1})	Acetylcholine (10 μmol litre^{-1})	Potassium chloride (40 mmol litre^{-1})
Diazepam	1.3×10^{-5}	3.6×10^{-5}	4.5×10^{-5}
Thiopentone	3.0×10^{-4}	2.1×10^{-4}	1.5×10^{-4}
Ketamine	1.3×10^{-3}	2.9×10^{-3}	4.7×10^{-4}
Morphine	3.4×10^{-4}	—	—
Propanidid	3.5×10^{-4}	4.1×10^{-4}	1.6×10^{-4}
Lignocaine	4.0×10^{-3}	3.5×10^{-3}	1.4×10^{-3}
Procaine	1.5×10^{-4}	3.7×10^{-5}	4.4×10^{-3}

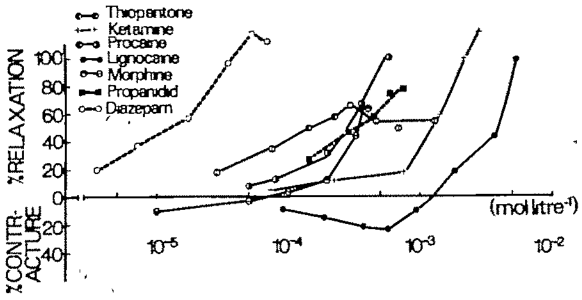


FIG. 2. The effects of anaesthetics on contractures induced in guineapig tracheal smooth muscle by histamine 10 μmol litre^{-1}. The results are expressed as a percentage relaxation or contracture in comparison with the contractures induced by the histamine. Per cent relaxation or contracture is shown on the vertical axis and the concentrations of the anaesthetic drugs are shown on the horizontal axis.

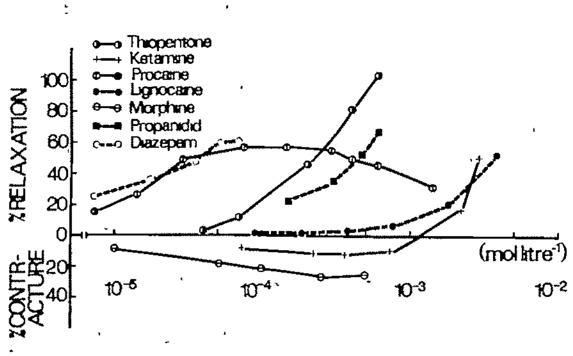


FIG. 3. The effects of anaesthetics on contractures induced in guineapig tracheal smooth muscle by acetylcholine 10 μmol litre^{-1}. The results are expressed as a percentage relaxation or contracture in comparison with the contractures induced by the acetylcholine. Per cent relaxation or contracture is shown on the vertical axis and the concentrations of the anaesthetic drugs are shown on the horizontal axis.

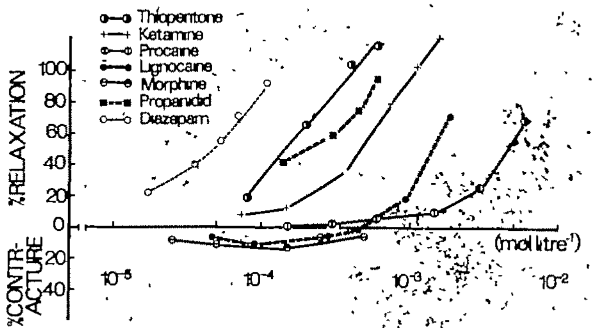


FIG. 4. The effects of anaesthetics on contractures induced in guineapig tracheal smooth muscle by potassium chloride 40 mmol litre^{-1}. The results are expressed as a percentage relaxation or contracture in comparison with the contractures induced by the potassium chloride. Per cent relaxation or contracture is shown on the vertical axis and the concentrations of the anaesthetic drugs are shown on the horizontal axis.

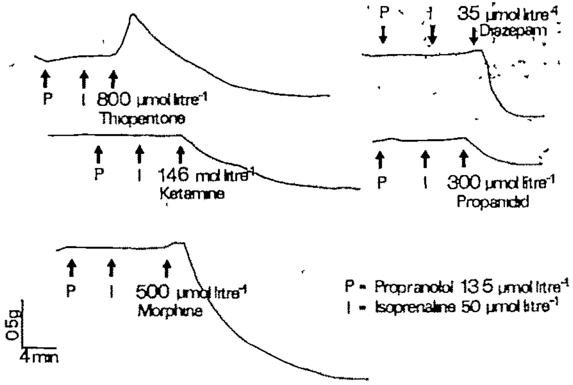


FIG. 5. Experiments showing that propranolol 13.5 μmol litre^{-1} blocks the relaxing effect of isoprenaline 50 μmol litre^{-1} in guineapig tracheal smooth muscle, but has no effect on the relaxation induced by thiopentone 800 μmol litre^{-1}, ketamine 1.46 mmol litre^{-1}, morphine 500 μmol litre^{-1}, diazepam 35 mmol litre^{-1} and propanidid 300 μmol litre^{-1}. Contracture and relaxation (g) are shown on the vertical axis and time (min) on the horizontal axis.

DISCUSSION

More is known about the effects of inhalation anaesthetics on airways smooth muscle than about the effects of anaesthetic drugs which are given i.v.

Halothane produces bronchodilatation in man (Meloche et al., 1969) and in the dog (Colgan, 1965). Methoxyflurane induces relaxation of the guineapig tracheal chain (Caujolle and Pham-Huu-Chanh, 1966). On the other hand, cyclopropane causes bronchoconstriction in dog lung (Colgan, 1965) and also when applied directly to bronchial slices from the rat, dog and man (Adriani and Rovenstine, 1943).

The present study has shown that, like most anaesthetics given by inhalation, most anaesthetic drugs which are given i.v. also induce relaxation of airways smooth muscle.

Clinically, the administration of diazepam may increase arterial $P\text{CO}_2$ in patients with chronic obstructive airways disease (Catchlove and Kafer, 1971), but does not cause an increase in Pa_{CO_2} in anaesthetized patients when ventilation is controlled (Heinonen and Muittari, 1972).

In the present investigation, diazepam relaxed guineapig tracheal smooth muscle and antagonized contractures induced by histamine, acetylcholine and potassium chloride. The amounts of diazepam needed to produce 50% antagonism of contractures were similar for each of these bronchoconstricting agents, and the effects of diazepam were not influenced by propranolol. The commercial preparation of diazepam used in these experiments contains propylene glycol, ethanol, benzyl alcohol, sodium benzoate and benzoic acid, and, although these agents may have influenced the results, it is clear that diazepam, in the form in which it is used clinically, causes relaxation of guineapig airways smooth muscle.

Thiopentone appears to have differing effects on airways smooth muscle from different species. It causes bronchoconstriction in excised lung tissue preparations from the rat, dog and man (Adriani and Rovenstine, 1943). This bronchoconstrictor effect is augmented by physostigmine and prevented by atropine. Previous studies in guineapig trachea have shown that thiopentone causes relaxation and antagonizes acetylcholine-induced contractures (Fletcher, Flacke, and Alper, 1968). In rabbit trachea, thiopentone appears to have no effect (Edney and Downs, 1975).

In the present study thiopentone, in concentrations similar to those used in human anaesthesia (250 μmol litre^{-1}), caused contracture of guineapig tracheal smooth muscle, but at concentrations greater than 400 μmol litre^{-1} it caused relaxation. Thiopentone antagonized contractures induced by histamine, acetylcholine and potassium chloride. The amounts of thiopentone needed to produce 50% relaxation of contractures were similar for each of these bronchoconstricting agents. The effect of thiopentone was not blocked by propranolol. The reason why thiopentone causes contraction at small concentrations and relaxation at large concentrations is not known. It is not because of a change in pH. Concentrations of barbiturate less than 1 mmol litre^{-1} do not effect the pH in Krebs solution (Edney and Downes, 1975). In the present study, the concentrations of thiopentone used were all less than 1 mmol litre^{-1}, and there was no change in pH in the Krebs solution.

From the practical point of view it is important to remember that, in the present investigation, clinical concentrations of thiopentone caused contracture in guineapig tracheal muscle. It has also been shown that thiopentone releases histamine in man (Lorenz et al., 1972).

Ketamine has been used safely in patients with asthma (Betts and Parking, 1971; Corssen et al., 1972), and airways resistance is reduced by the administration of ketamine to patients with asthma, although it does not have this effect in non-asthmatic patients (Huber et al., 1972). Using guineapig tracheal smooth muscle preparations, Lundy, Gowdey and Colhoun (1974) found that ketamine had a direct relaxant effect, that it antagonized contractures induced by carbachol and potentiated the relaxing effect of adrenaline. Similar observations were made in the present investigation.

Morphine has long been known to have a bronchoconstricting effect (Higgins and Meann, 1915; Jackson, 1916). In the present investigation morphine, at concentrations about 10 times greater than the clinical dose, induced relaxation of guineapig tracheal smooth muscle. It also relaxed histamine-induced contractures of tracheal smooth muscle, but had no effect on acetylcholine or potassium chloride-induced contractures. It seems that morphine exerts its bronchoconstrictor effect by histamine release, by histamine-induced axon reflex which increases vagal tone, and by a direct action on the medullary bronchoconstrictor centre (Aviado, 1975).

A commercial preparation of propanidid (Epontol) induced relaxation of guineapig tracheal smooth muscle and antagonized contractures induced by histamine, acetylcholine and potassium chloride in the present investigation, although i.v. injection of propanidid for anaesthesia increases the blood histamine concentration (Lorenz et al., 1972). Epontol contains 16% of a butyl alcohol extract of polyethoxylated castor oil, and the effect of this on the responses obtained is not known.

Lignocaine, at concentrations less than 1 mmol litre^{-1}, induced contractures in guineapig tracheal preparations, but produced relaxation at concentrations greater than this. Lignocaine, at concentrations greater than 1 mmol litre^{-1}, antagonized contractures induced by histamine, acetylcholine and potassium chloride. Lignocaine 1 mmol litre^{-1} is about 10 times more concentrated than would be reached by the usual clinical dose. Similar observations have been made by Weiss, Anderson and O'Brien (1975) and Downes and Loehning (1977).

Clinically, it has been suggested that lignocaine applied topically to the airways is effective in preventing bronchospasm (Pelton et al., 1970), and that the i.v. administration of lignocaine can abolish bronchospasm (Brandus et al., 1970). Ultrasonically nebulized lignocaine has also been reported to antagonize the increased respiratory resistance induced by nebulized water (Loehning, Waltemath and Bergman, 1976). It is not known whether the action of lignocaine in preventing bronchospasm in humans is a direct action on smooth muscle, or a central action as inhibition of the vagal reflex or respiratory cough reflex.

Although an earlier study found that procaine caused relaxation of an isolated tracheal preparation (Macht and Ting, 1921), in the present investigation procaine consistently induced contracture of guineapig tracheal smooth muscle and produced rhythmical contracture and relaxation. Different concentrations of procaine were required to produce 50% relaxation of contractures induced by histamine, acetylcholine and potassium chloride.

Although guineapig tracheal smooth muscle and human tracheal smooth muscle are pharmacologically similar *in vitro*, caution should be exercised in applying the results of the present investigations to man. It is possible also that reactions in tracheal smooth muscle may differ from those in bronchial smooth muscle (Fleisch and Calkins, 1976; Lulich, Mitchell and Sparrow, 1976).

REFERENCES

Adriani, J., and Rovenstine, E. A. (1943). The effect of anesthetic drugs upon bronchi and bronchioles of excised lung tissue. *Anesthesiology*, **4**, 253.

Akcasu, A. (1959). The physiologic and pharmacologic characteristics of the tracheal muscle. *Arch. Int. Pharmacodyn.*, **122**, 201.

Aviado, D. M. (1975). Regulation of bronchomotor tone during anesthesia. *Anesthesiology*, **42**, 68.

Betts, E. K., and Parking, C. E. (1971). Use of ketamine in an asthmatic child: a case report. *Anesth. Analg. (Cleve.)*, **50**, 420.

Brandus, V., Joffe, S., Benoit, C. V., and Wolff, W. I. (1970). Bronchial spasm during general anaesthesia. *Can. Anaesth. Soc. J.*, **17**, 269.

Catchlove, R. F. H., and Kafer, E. R. (1971). The effects of diazepam on respiration in patients with obstructive pulmonary disease. *Anesthesiology*, **34**, 14.

Caujolle, F., and Pham-Huu-Chanh, X. (1966). Effets des aérosols de bromo-2-chloro-2-trifluoro-1, 1, 1-éthane (Halothane) et de l'éther oxyde mixte de méthyle et de difluoro-1, 1-dichloro-2, 2-éthyle (méthoxyflurane) sur les poumons isolés de cobaye. *Méd. Pharmacol. Exp.*, **15**, 419.

Colgan, F. J. (1965). Performance of lungs and bronchi during inhalation anesthesia. *Anesthesiology*, **26**, 778.

Corssen, G., Gutierrez, J., Reeves, J. G., and Huber, F. C. (1972). Ketamine in the anesthetic management of asthmatic patients. *Anesth. Analg. (Cleve.)*, **51**, 588.

Downes, H., and Loehning, R. W. (1977). Local anesthetic contracture and relaxation of airway smooth muscle. *Anesthesiology*, **47**, 430.

Edney, S. M., and Downes, H. (1975). Contractor effect of barbiturates on smooth muscle. *Arch. Int. Pharmacodyn.*, **217**, 180.

Fleisch, J. H., and Calkins, P. J. (1976). Comparison of drug-induced responses of rabbit trachea and bronchus. *J. Appl. Physiol.*, **41**, 62.

Fletcher, S. W., Flacke, W., and Alper, M. H. (1968). The actions of general anesthetic agents on tracheal smooth muscle. *Anesthesiology*, **29**, 517.

Heinonen, J., and Muittari, A. (1972). The effect of diazepam on airway resistance in asthmatics. *Anaesthesia*, **27**, 37.

Higgins, H., and Meann, J. (1915). The effect of certain drugs on the respiratory and gaseous metabolism in normal human subjects. *J. Pharmacol. Exp. Ther.*, **7**, 1.

Huber, F. C. jr, Reves, J. G., Gutierrez, J., and Corssen, G. (1972). Ketamine: its effect on airway resistance in man. *South. Med. J.*, **65**, 1176.

Jackson, D. E. (1916) The peripheral action of opium alkaloids with special reference to the bladder. *J. Lab. Clin. Med.*, **1**, 862.

Loehning, R. W., Waltemath, C. L., and Bergman, N. A. (1976). Lidocaine and increased respiratory resistance produced by ultrasonic aerosols. *Anesthesiology*, **44**, 306.

Lorenz, W., Doenicke, A., Meyer, R., Reimann, H. J., Kusche, J., Barth, H., Geesing, H., Hutzel, M., and Weissenbacher, B. (1972). Histamine release in man by propanidid and thiopentone: pharmacological effects and clinical consequences. *Br. J. Anaesth.*, **44**, 355.

Lulich, K. M., Mitchell, H. W., and Sparrow, M. P. (1976). The cat lung strip as *in vitro* preparation of peripheral airways: a comparison of β-adrenoceptor agonists, autocoids and anaphylactic challenge on the lung strip and trachea. *Br. J. Pharmacol.*, **58**, 71.

Lundy, P. M., Gowdey, C. W., and Colhoun, E. H. (1974). Tracheal smooth muscle relaxant effect of ketamine. *Br. J. Anaesth.*, **47**, 333.

Macht, D. I., and Ting, G. (1921). A study of antispasmodic drugs on the bronchus. *J. Pharmacol. Exp. Ther.*, **18**, 373.

Meloche, R., Norlander, O., Norden, I., and Herzog, P., (1969). Effects of carbon dioxide and halothane on compliance and pulmonary resistance during cardiopulmonary bypass. *Scand. J. Thorac. Cardiovasc. Surg.*, **3**, 69.

Pelton, D. A., Daly, M., Cooper, P. D., and Conn, A. W. (1970). Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. *Can. Anaesth. Soc. J.*, **17**, 250.

Weiss, E. B., Anderson, W. H., and O'Brien, K. P. (1975). The effect of a local anaesthetic, lidocaine, on guineapig trachealis muscle *in vitro*. *Am. Rev. Respir. Dis.*, **112**, 393.

EFFETS DES AGENTS ANESTHESIANTS SUR LE MUSCLE LISSE TRACHEAL DU COBAYE

RESUME

On a fait des recherches *in vitro* sur les effets qu'ont les anesthésiants administrés par voie intraveineuse et les anesthésiants locaux sur le muscle lisse trachéal du cobaye. Le diazépam, le propanidid et la kétamine entraînent la relaxation et contrarient les contractions du muscle lisse trachéal provoquées par l'histamine, l'acétylcholine et le chlorire de potassium. Les effets relaxants des agents anesthésiants n'ont pas été affectés par le propranolol. Le thiopentone, aux concentrations que l'on utilise cliniquement, entraîne une contraction du muscle lisse trachéal. La morphine provoque la relaxation et contrarie la contraction provoquée par l'histamine, mais ne contrarie pas les contractions provoquées par l'acétylcholine ou le chlorure de potassium. La lignocaïne et la procaïne, aux concentrations cliniques, provoquent une contraction du muscle lisse trachéal. Les fortes doses de lignocaïne relaxent le muscle trachéal, mais les fortes doses de procaïne provoquent des mouvements rythmiques spontanés. La lignocaïne et la procaïne contrarient les contractions provoquées par l'histamine, l'acétylcholine et le chlorure de potassium.

WIRKUNGEN VON ANÄSTHESIEMITTEL AUF DIE GLATTE TRACHEALMUSKULATUR VON MEERSCHWEINCHEN

ZUSAMMENFASSUNG

Die Wirkungen lokaler und intravenoser Anästhesiemittel auf die glatte Trachealmuskulatur von Meerschweinchen wurden *in vitro* untersucht. Diazepam, Propanidid und Ketamin bewirkten Entspannung und wirkten dem von Histamin, Acethylcholin und Kaliumchlorid verursachten Kontraktionen der glatten Trachealmuskulatur entgegen. Die Entspannungswirkung der Narkosemittel wurde durch Propanolol nicht beeinträchtigt. Thiopenton verursachte in klinisch angewendeten Dosen eine Kontraktion der glatten Trachealmuskulatur. Morphium bewirkte Entspannung und hob die von Histamin verursachte Kontraktion auf, nicht aber die von Acetylcholin oder Kaliumchlorid verursachten. Lignocain und Procain in klinischen Konzentrationen bewirkten Kontraktionen der glatten Trachealmuskulatur. Grosse Dosen von Lignocain entspannten diese Muskeln, grosse Dosen von Procain bewirkten spontane rhytmische Bewegungen. Lignocain und Procain wirkten den von Histamin, Acetylcholin und Kaliumchlorid verursachten Kontraktionen entgegen.

EFECTOS DE LOS ANESTETICOS EN EL MUSCULO LISO TRAQUEAL DEL COBAYO

SUMARIO

Se averiguó *in vitro* los efectos de anestéticos locales e i.v. en el músculo liso traqueal del cobayo. El diazepam, el propanidido y la quetamina indujeron la relajación y antagonizaron las contracturas del músculo liso traqueal inducidas por la histamina, la acetilcolina y el cloruro de potasio. Los efectos relajantes de los anestéticos no fueron afectados por el propranolol. La tiopentona, en concentraciones en que se usaría clínicamente, causó contractura del músculo liso traqueal. La morfina indujó relajación y antagonizó la contracture inducida por la histamina, pero no antagonizó las contracturas inducidas por la acetilcolina o el cloruro de potasio. La lignocaina y la procaina, en concentraciones clínicas, indujeron contractura del músculo liso traqueal. Grandes dosis de lignocaina relajaron el músculo traqueal, pero grandes dosis de procaina indujeron movimientos rítmicos espontáneos. La lignocaina y la procaina antagonizaron las contracturas inducidas por la histamina, la acetilcolina y el cloruro de potasio.

Br. J. Anaesth. (1980), **52**, 205

MATURATION OF NEUROMUSCULAR TRANSMISSION IN THE INFANT

N. G. GOUDSOUZIAN

SUMMARY

Twitch tension, train-of-four and tetanus—clinical parameters of neuromuscular transmission—were studied in 37 infants and children anaesthetized with halothane. The contraction time was slower in infants less than 1 month old when compared with their elder counterparts. This may indicate a possible transformation from slow to faster muscle types. The train-of-four reached 100% in most of the infants older than 2 months. The post-tetanic facilitation and the tetanus : twitch ratios were significantly greater in infants older than 2 months when compared with infants less than 1 month. Post-tetanic exhaustion was seen in all the infants and children after stimulation at 100 Hz. Tetanus : twitch ratios were greater in infants more than 2 months old and in children, and the tetanic force was more marked at 50 Hz than at 20 Hz. The data indicate that maturation of neuromuscular transmission occurs in infants in and around the first 2 months of age.

Neuromuscular transmission has been observed to be less mature in newborn infants than in adults. Early in 1963, Churchill-Davidson and Wise demonstrated by electromyography that, at twitch rates (0.25 Hz), neuromuscular transmission was well maintained in infants, but at tetanic rates (50 Hz) it was poorly maintained. Some infants demonstrated post-tetanic exhaustion. Koenigsberger, Patten and Lovelace (1973) made a similar observation. They also found that fading tetanus and post-tetanic exhaustion were more marked in the premature infant.

On the basis of these studies, it was difficult for us to evaluate the neuromuscular status in infants at the end of surgical procedures after the antagonism of non-depolarizing muscle relaxants. Therefore, after anaesthetizing the infants and children, we recorded the parameters clinically accepted for evaluating neuromuscular transmission—force of contraction of the adductor of the thumb in response to slow (0.25 Hz and 2 Hz) and rapid (20 Hz and 50 Hz) rates of stimulation—and then administered the muscle relaxants. These data enabled us to monitor closely the neuromuscular status of these infants and children during and after the surgical procedure.

This study reports the neuromuscular transmission in 37 infants and children before the administration of neuromuscular blocking drugs and the changes of neuromuscular transmission which occur with the growth of the infant.

METHODS

Thirty-seven infants and children undergoing general surgery were studied. They ranged from newborn full-term babies to children 9 years of age. Premedication consisted of rectal methohexitone 20 mg kg^{-1} in children more than 1 yr of age. No premedication was given to younger patients.

Anaesthesia was induced with a face-mask using a 2 : 1 mixture of nitrous oxide and oxygen followed by halothane from a Fluotec Mark 2 vaporizer. Mean inspired halothane concentration was recorded in all patients. Tracheal intubation was performed without neuromuscular blocking agents. In infants less than 4 weeks of age, intubation was performed before the administration of the anaesthetic. The electrocardiogram and temperature were monitored. Oesophageal temperature was kept between 35.5 °C and 37 °C. Anaesthesia was maintained with halothane (1–2% inspired), 60% nitrous oxide in oxygen using a humidified Ayres' T-piece in infants and the circle system in children.

Neuromuscular transmission was studied with a Grass FT-03 force displacement transducer. The hand of the child was attached firmly on a padded metal board with adhesive tape. The thumb was taped to a small wooden stick trimmed to the size of the infant's thumb. This in turn was connected by silk thread to the force displacement transducer. The transducer was mounted on the metal board. Care was taken that the direction of the force of contraction was perpendicular to the transducer. The duration of electrical impulse was 0.2 ms, generated by a Grass S44 stimulator. The force of contraction of the

---

N. G. GOUDSOUZIAN, M.D.; Department of Anaesthesia, Harvard Medical School at the Massachusetts General Hospital, Boston, Massachusetts 02114, U.S.A.

0007–0912/80/020205–10 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Summary of the results obtained in the infants and children studied. The number of patients in each group is in parenthesis*

	Contraction time (ms)	Train-of-four (%)	Tetanus 20 Hz			Tetanus 50 Hz			Tetanus 100 Hz			Height of tetanus (mm)		
			Fade (%)	PTF (%)	Tetanus : twitch ratio	Fade (%)	PTF (%)	Tetanus : twitch ratio	Fade (%)	PTF (%)	Tetanus : twitch ratio	20 Hz	50 Hz	100 Hz
Group I	73.3	95.3	3.8	5.1	3.5	7.3	3.9	4.1	19	−19.4	3.8	25.1	29.8	29
1 month	±3.4	±0.7	±0.9	±.28	±0.2	±1	±2.9	±0.2	±4	±6.6	±0.2	±2	±2.4	±3
or less	(11)	(11)	(11)	(11)	(11)	(11)	(10)	(11)	(7)	(7)	(8)	(11)	(11)	(7)
Group II	56.6	99.1	5.8	13.7	5.5	9.6	22.6	6.9	14.6	−14.3	4.2	27	32	31.8
2 months	±1.4	±0.3	±1.1	±1.9	±0.3	±1.1	±4.8	±0.5	±2.3	±0.5	±0.3	±1.3	±1.6	±5.9
–9 yr	(21)	(22)	(22)	(22)	(22)	(22)	(22)	(22)	(10)	(10)	(11)	(22)	(22)	(6)
P (between groups)	<0.001	<0.001	n.s.	<0.01	<0.001	n.s.	<0.001	<0.001	n.s.	n.s.	n.s.	—	—	—
Mean of all	62.1	97.7	5.4	10.5	4.8	9.1	18.6	5.9	16.7	−16.3	4.2	—	—	—
patients	±1.9	±0.4	±0.7	±1.6	±0.2	±0.8	±3.5	±0.4	±2	±3.9	±0.2			
studied	(36)	(37)	(37)	(37)	(37)	(37)	(36)	(37)	(17)	(17)	(17)			

thumb in response to indirect square-wave supramaximal stimuli applied at the ulnar nerve at 0.25 Hz, at 2 Hz for 2 s (train-of-four stimulation), and at 20, 50 and 100 Hz for 5 s (tetanic stimulation) was recorded on a Grass polygraph. During the study, sufficient time was allowed between each tetanic stimulus for recovery of the twitch height to its normal pre-tetanic value. Stimulation at 20 Hz was repeated to verify that it was similar to the first one and that the changes observed were not a result of exhaustion of the myoneural junction (fig. 1).

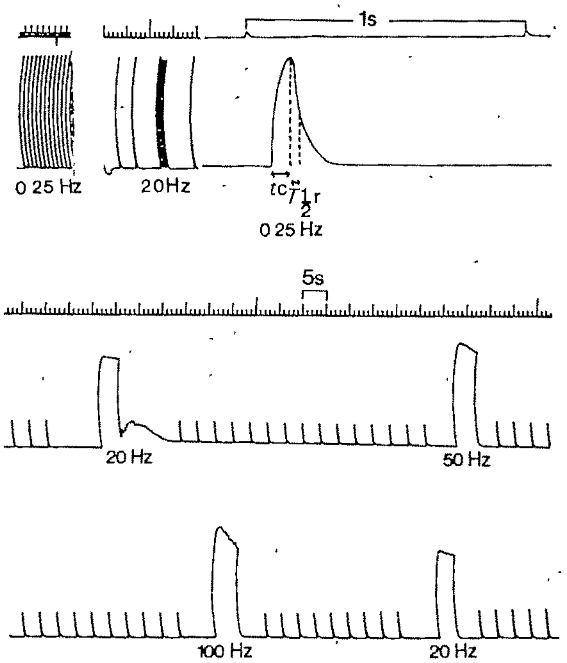


FIG. 1 A typical recording of the force of contraction of the thumb in response to supramaximal ulnar nerve stimulation. The rates of stimulation are: 0.25 Hz, 2.0 Hz for 2 s, 20, 50, 100 Hz for 5 s alternating with 0.25 Hz.

The following data were measured:

(1) Contraction time (*tc*) at twitch rates of stimulation (0.25 Hz): the time interval from the beginning of thumb adduction to maximum developed tension.

(2) Half relaxation time at twitch rates of stimulation ($T_{\frac{1}{2}}r$): relaxation time from maximum point of twitch height to 50% of the maximum developed tension.

(3) The train-of-four ratio: the per cent ratio of the height of the fourth twitch to the height of the first in the train-of-four at 2 Hz.

(4) The per cent tetanic fade: the per cent ratio of the decrease in height of tetanic force after 5 s of stimulation to the height of the initial force of tetanus.

(5) Per cent post-tetanic facilitation (PTF): the per cent change in the height of post-tetanic twitch after the tetanus relative to the height of pre-tetanic twitch. The time interval between the end of tetanus and post-tetanic twitch was 6–8 s.

(6) Tetanus : twitch ratio: the ratio of the height of tetanus to the pretetanic twitch height.

(7) Tetanic heights at 20 Hz, 50 Hz and 100 Hz: the height of tetanus at 20 Hz was compared with the height of tetanus at 50 Hz and 100 Hz.

Initially, the latter three parameters were determined at 20 Hz, 50 Hz, and 100 Hz. However, after evaluating the initial 19 determinations, we found that the results obtained from stimulation at 100 Hz were uninformative because of the marked fade and post-tetanic exhaustion; therefore, we discontinued recording this parameter.

The statistical analysis was performed by using the correlated, non-correlated Student *t* test and correlation coefficient. The correlated *t* test was used when data for comparison were on the same patients, whereas the non-correlated test was used for analysis between different groups of patients. The values were considered significant when $P < 0.05$ and highly significant when $P < 0.005$.

RESULTS

When the data were arranged according to age of the infants and children, we noticed a distinguishable difference in the parameters between infants less than 1 month of age and infants older than 2 months, an overlap occurring between 1 and 2 months. Consequently, we divided the data into two groups according to age (table I).

Group I. Infants less than 1 *month old.* Eleven full-term infants from the 1st day of life to 30 days.

Group II. Patients older than 2 *months.* Twenty-two infants and children from 61 days to 9 years.

The four infants 1–2 months old were excluded from the statistical analysis when the comparison was made between groups I and II. However, they were included for the correlation analysis of all the infants and children studied.

Halothane concentration

The halothane concentration in the first group of infants was 1.2±0.1% and in the second group it was 1.3±0.1%. There was no significant difference between the values of the two groups.

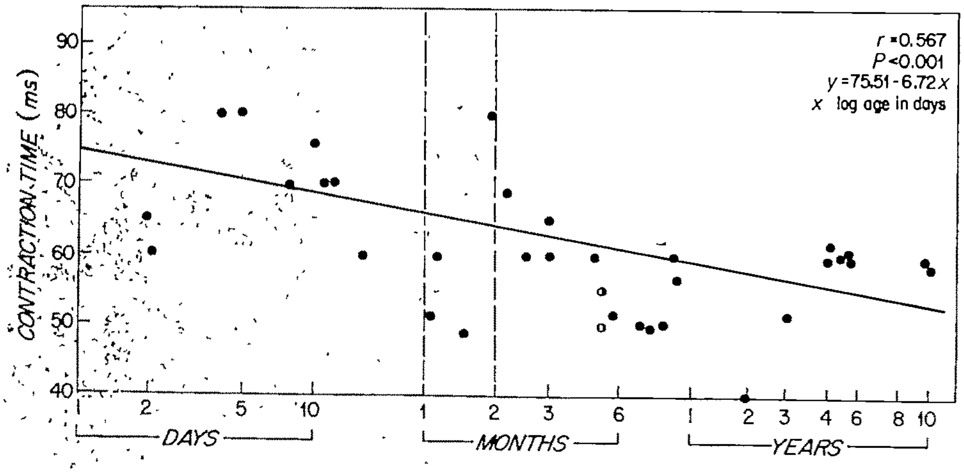


FIG. 2. Individual contraction times (ms) of the adductor of the thumb in response to supramaximal twitch rates of stimulation (0.25 Hz). Age in days is plotted on logarithmic scale on abscissa.

Contraction time (*tc*)

There was a significant negative correlation (r = 0.56, $P < 0.005$) between age of the child and contraction time, *tc* decreasing with the growth of the infant (fig. 2). In group I, *tc* was 73.3 ± 3.4 ms (mean ± SEM) and in group II it was 56.6 ± 1.4 ($P < 0.005$).

Half relaxation time ($T_{\frac{1}{2}}$r)

There was no significant correlation of the half relaxation time with age nor was there any difference between the two groups. The mean half relaxation time of all patients studied was 38.5 ± 1.5 ms.

Train-of-four

The train-of-four values increased significantly with the growth of the infant ($r = 0.65$, $P < 0.001$) from the minimum 93% to 100% value in most of the infants older than 2 months (fig. 3). The difference between the two groups was analysed using the Student's t test for the mean values of the train-of-four and with the Chi-square test for the number of infants or children who had reached 100% values. The difference between the two groups by these two methods was highly significant ($P < 0.001$).

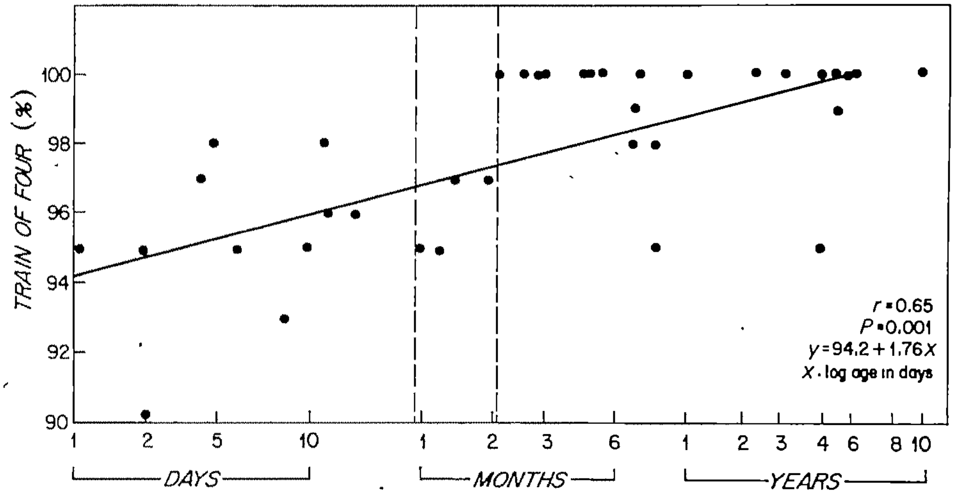


FIG. 3. Train-of-four values in the infants and children studied. Note that most of the children older than 2 months have a train-of-four value of 100%.

Fade of tetanus at 20 Hz, 50 Hz and 100 Hz

There was no significant correlation of the fade of tetanus with age of the infants between group I and group II infants at 20 Hz, 50 Hz and 100 Hz. However, the degree of fade increased significantly ($P < 0.01$) in each child when the rate of stimulation was increased from 20 Hz to 50 Hz and 100 Hz (fig. 4).

Post-tetanic facilitation

There was a significant positive correlation between the age of the child and post-tetanic facilitation. The correlation was more marked for PTF after 50 Hz ($r = 0.5$, $P < 0.005$) than after 20 Hz ($r = 0.44$, $P < 0.01$) (fig. 5). In group I infants, increasing the rate of tetanic stimulation from 20 Hz to 50 Hz did not lead to an increase in PTF. However, in group II, increasing the rate of tetanus led to a significant increase in the amount of PTF ($P < 0.02$). Increasing the rate of tetanus further to 100 Hz led to the opposite effect—the twitch after 100 Hz was less than the pre-tetanic twitch, indicating the occurrence of post-tetanic exhaustion (fig. 6).

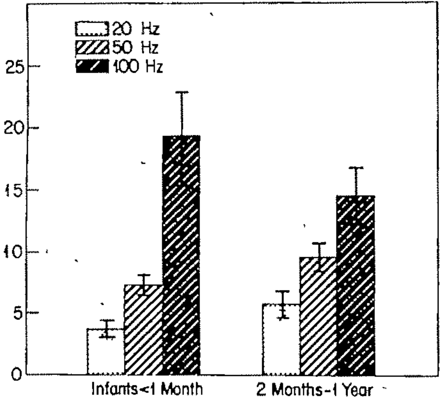


FIG. 4. Per cent fade (means ± SEM) in the two groups of infants and children studied. Note the increased fade upon increasing the rate of stimulation from 20 Hz to 50 Hz and 100 Hz.

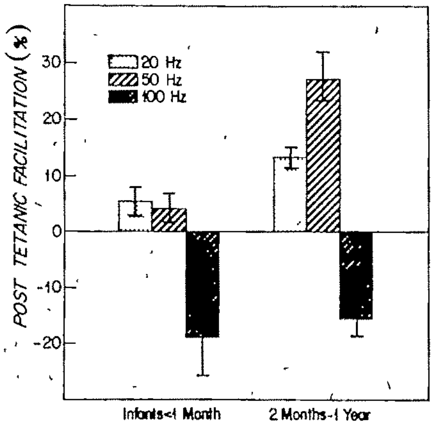


FIG. 5. Per cent post-tetanic facilitation in the individual infants and children studied at 20 Hz and 50 Hz. Note the steeper rise of the rate of fade at 50 Hz than at 20 Hz.

Tetanus: twitch ratio

The tetanus : twitch ratio is the parameter that showed a high correlation with age at 20 Hz ($r = 0.65$, $P \leqslant 0.001$) and at 50 Hz ($r = 0.5$, $P < 0.005$) (fig. 7). Between the two groups, the tetanus : twitch ratio was significantly greater in group II (5.5 ± 3 at 20 Hz, 6.9 ± 0.5 at 50 Hz) than in group I infants (3.5 ± 0.2 at 20 Hz and 4 ± 0.2 at 50 Hz).

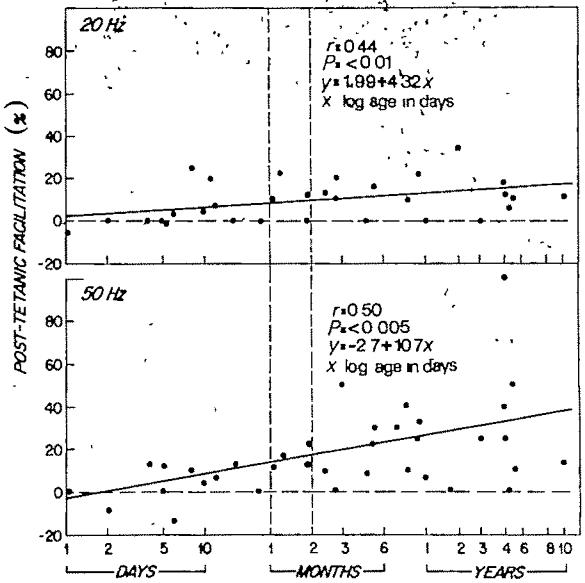


FIG. 6. Per cent post-tetanic facilitation in the two groups of infants and children. Note the marked increase of PTF at 50 Hz relative to 20 Hz in the older group of infants and children, also the negative values of PTF after 100 Hz in both of the groups indicating post-tetanic exhaustion.

Height of tetanus

The height of tetanus increased significantly ($P < 0.001$) upon increasing the stimulation rate from 20 Hz to 50 Hz. Increasing the rate of stimulation to 100 Hz did not produce any further increase in the height of tetanus (fig. 8).

Our results indicate that contraction time diminishes with age, whereas the values for train-of-four, post-tetanic facilitation and tetanus : twitch

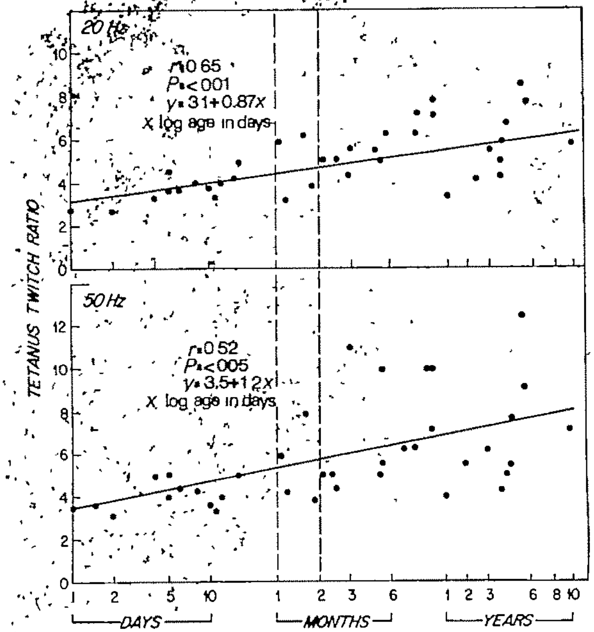


FIG. 7. Tetanus : twitch ratio at 20 Hz and 50 Hz tetanic rates of stimulation.

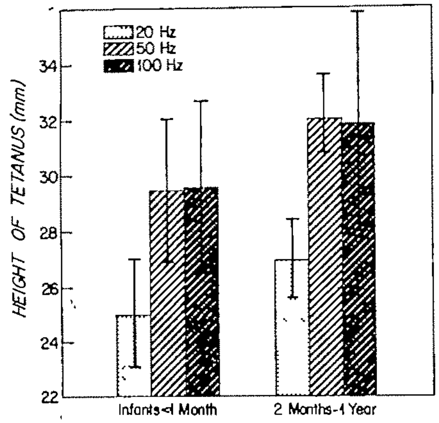


FIG. 8. The height of tetanus in response to 20 Hz, 50 Hz and 100 Hz of stimulation. Of note is the significant ($P < 0.001$) increase in the height of tetanus upon increasing the rate of stimulation from 20 Hz to 50 Hz and no further increase at 100 Hz.

ratios increased with age. These neuromuscular parameters were highly significantly different between infants less than 1 month and patients older than 2 months, an overlap occurring in the 1st month of extrauterine life.

DISCUSSION

Contraction time

The progressive decline in contraction time with the growth of the infant can be explained as follows. During the early days of extrauterine life, muscle fibres undergo metabolic and structural changes and are transformed from slow twitch types, type I (slow-twitch-oxidative), to fast twitch types, type II (fast-twitch-oxidative-glycolytic and fast-twitch-glycolytic) (Curless, 1977).

This conversion from slow to fast muscles has been demonstrated in animals. Close (1964) studied the velocity properties of the newborn rat soleus muscle, a slow muscle, and extensor digitorum longus, a fast muscle. In the 1st day of life, the velocity properties of these two types of muscle are the same. However, in the subsequent 5 weeks of extrauterine growth, the speed of shortening per sarcomere increased 2.5–3 times in the extensor digitorum longus, whereas in the soleus it remained the same. This study was confirmed by Brown (1973). This transformation from slow to fast muscles has been demonstrated in kittens (Buller and Eccles, 1960).

This change of pattern from slow to fast types has not been demonstrated in humans. However, other types of change have been demonstrated such as increase in size of muscle fibres (Dubowitz, 1968). In contrast, Brooke and Kaiser (1970) found an equal distribution of slow and fast muscle fibres. However, their biopsy specimens were obtained from infants with cerebral anomalies, and animal studies have shown that slow fibres are less dependent on neural influences than fast fibres (Engel and Karpati, 1968). The cerebral condition may have slowed down the maturation of type II fibres.

Recently Keens and others (1978), using histochemical techniques, found that the diaphragm of the full-term newborn baby had only 25% type I (slow) fibres and the percentage of slow muscles reached their maximum at the age of 8 months (55%). In the intercostal muscles, the proportion of slow muscle fibres was different, as was the rate of change. At term, they contained 46% slow muscles, which increased to the maximum (65%) at 2 months of age. In their study, the change was opposite to that recorded in our study—fast muscles changing to slow type. This is probably because respiratory muscles have to adapt to work for sustained periods of time without showing fatigue. Interestingly, in our study the shift from slow to fast muscle type occurred mostly before the age of 2 months—the age at which the intercostal muscles showed their ultimate change.

We cannot offer a complete explanation for the change of contraction time that we observed in the infants. It may be a result of changes in contraction properties as has been suggested by Gatev and others (1975) when they noticed that, in infants less than 9 months, tetanus was fused more easily than in the older children with submaximal stimuli at 30 Hz. However, to prove definitely that it is a result of transformation from slow (type I) to fast (type II) muscles is beyond the scope of this study.

Train-of-four

The train-of-four has proved to be a satisfactory way of evaluating neuromuscular blockade without the need for a control response. The low frequency (2 Hz) is rapid enough to produce significant depletion of the immediately available stores of acetylcholine and yet slow enough to prevent transmitter facilitation (Ali and Savarese, 1976). There is a highly significant positive linear association between the ratio of the fourth to the first response in the train and the ratio of first response in the same train to the control response in adults (Ali, Utting and Gray, 1971) and in infants and children (Goudsouzian et al., 1975). The train-of-four is considered more sensitive than the twitch height for evaluating neuromuscular blockade, but is less sensitive than the tetanus. In our study, we notice that infants less than 2 months of age had a lower value of train-of-four than older infants. This might be an indication of the lesser maturity of the neuromuscular transmission in infants less than 2 months of age.

Fade

Increasing the rate of tetanic stimulation from 20 Hz to 50 Hz and 100 Hz led to an increase in the degree of fade ($P < 0.01$) in all the infants and children studied (fig. 4). Our results are comparable to those reported in adults anaesthetized with nitrous oxide in oxygen (Stanec et al., 1978). In adults, tetanic fade at 50 Hz for 5 s was 5% and at 100 Hz was 20%. In our present study in children anaesthetized with halothane, the comparable figures were 9% and 17% at 20 Hz and 50 Hz respectively.

Contrary to our expectations and previous findings, we did not note a tendency for the rate of fade to be greater in smaller infants. Churchill-Davidson (1963) reported marked fade in five infants after 20 s of stimulation. Similarly, Koenigsberger, Patten and Lovelace (1973) noticed a marked fade in infants after 15 s of stimulation; and this fade was more marked in premature infants. The discrepancy in our results can be explained in that the duration of our tetanic stimulation was relatively short (5 s), whereas the other studies used 15–20 s of stimulation. Therefore, in our study there was no chance for marked fatigue to develop in the infants. Also, at high frequencies of stimulation in the early stages, facilitation on electromyography had been observed; thus, our results might have been masked by this facilitation competing with fatigue.

Post-tetanic potentiation (PTP)

The most plausible explanation for the presence of PTP is that mobilization and enhanced synthesis of acetylcholine continue during and after cessation of tetanic stimulation. Therefore, the readily releasable fraction (the quantal content) is increased at the end of tetanus (Ali and Savarese, 1976).

When there is no diminution of the margin of safety, this increased quantal production will not cause PTP because all the muscle fibres are maximally excited. However, when the integrity of the myoneural junction is impaired, the pre-tetanic twitch is submaximal. With the increase of post-tetanic quantal content, a larger number of muscle fibres may be excited by the nerve stimulation, thus producing the PTP. In kittens (Standaert, 1964) the mechanism of PTP seems to differ according to the nerve or muscle studied. In the ulnar nerve, post-tetanic repetitive activity originates in the motor nerve and is transmitted to the muscle. However, in the gastrocnemius muscle, the post-tetanic repetitive activity occurs too infrequently and even occurs in directly curarized, directly stimulated muscle, indicating a muscle phenomenon. In the adult man, PTP is only seen when the force of contraction (mechanical events) is recorded; it is not seen with electromyography (Epstein and Epstein, 1973; Katz, 1973).

This increase in mechanical activity beyond the increase in electrical activity has been demonstrated by Gatev and others (1975) in children aged $2\frac{1}{2}$–3 years old and was absent in children less than 9 months old. However, in their study, the intensity of stimulation was submaximal (20% of supramaximal).

The degree of PTP varies with the frequency of stimulation and the duration of tetanus as well as with the post-tetanic interval. Adults, at high rates of stimulation (100 Hz), show post-tetanic *exhaustion* (Stanec et al., 1978). The children showed a similar tendency in our study, thus rendering the clinical usefulness of this rate of stimulation (100 Hz) for evaluating the adequacy of neuromuscular transmission minimal. In our study, PTP was more marked at 50 Hz than at 20 Hz (with marked individual variations).

Tetanus : twitch ratio

The tetanus : twitch ratio is a parameter that has been used infrequently, despite the fact that it is very easy to record and to evaluate. In animal studies (Close, 1964), it has shown to be very valuable for ascertaining the development of muscles.

In our present study, we found a strong correlation between the age of the child and the tetanus : twitch ratio. In infants less than 1 month old, at 20 Hz the tetanic height was 3.5 times more than the twitch height; in older infants, it was 5.5 times more. The same trend was present at stimulation of 50 Hz, the values being 4.1 in small infants and 6.9 in the older group. The greater ratios at 50 Hz indicate that the myoneural junction is more stressed at this frequency. However, further increasing the rate of tetanic stimulation to 100 Hz did not lead to any more increase in the tentanus : twitch ratio.

The same relationship was apparent when we compared the individual height of tetanus in each child at 20 Hz, 50 Hz and 100 Hz. The height of tetanus increased upon increasing the rate of stimulation from 20 Hz to 50 Hz without any further increase at 100 Hz.

The most important overall observation of this study is that the maturation of neuromuscular transmission occurs in the first 2 months of age—newborns have less neuromuscular reserve than older children. The site of this deficiency can be at either the neuromuscular junction or the muscle itself. Animal studies have suggested both. Close (1964) found in growing animals an increase in the total number of tension-generating sites in parallel, a decrease in active state, and no change in the maximum force developed at each site. This mechanism can explain the increase in tetanus : twitch ratios that we observed. Kelly and Roberts (1977) found a diminution in the safety factor of the diaphragm of young rats as indicated by an increase in miniature end-plate potentials and a decrease in quantum content of the first end-plate potential of the train-of-four. This mechanism can explain the smaller values of train-of-four observed in our study. This decrease in quantal content will probably decrease the amount of acetylcholine release after the tetanic rate has been stopped, leading to the diminution of PTF observed. In summary, factors in the muscle itself as well as at the myoneural junction seem to affect the differences in neuromuscular transmission observed in our study.

The results of this report on first sight might seem to contradict our previous reports on non-depolarizing muscle relaxants in infants and children. We demonstrated, in studies of tubocurarine (Goudsouzian et al., 1975) and metocurine (Goudsouzian, Liu and Savarese, 1978) that infants and children have superimposed dose–response curves with marked individual variations in dose requirement when the dose of the non-depolarizing muscle relaxant has been calculated according to weight of the child. Previous studies which have measured muscle relaxation by observing respiration or clinical requirement have concluded that the newborn infants require less drug.

In this study we present evidence that the neuromuscular transmission is less developed in infants less than 1 month old. Is the neuromuscular junction of the infant more sensitive to non-depolarizing agents because it is less developed than the adult? Obviously, one cannot come to a definite conclusion from this study. There are several other factors which affect the pharmacokinetics of drugs in infants. The most important is the large extracellular volume of infants. In a newborn, it is 40% of body weight, whereas in an adult it is 18%. To reach the neuromuscular junction drugs have to distribute themselves in the extracellular space; drugs administered to an infant are distributed in a larger pool and a smaller concentration is achieved at the neuromuscular junction. This theory has been given as an explanation for the larger amount of depolarizing neuromuscular blocking drugs required by an infant (Cook and Fischer, 1978).

Based on the previous observations, the clinician interested in evaluating neuromuscular transmission in infants will obtain adequate information by stimulating at 0.25 Hz, 2 Hz for 2 s and 50 Hz for 5 s. From the train-of-four values, he can obtain a numerical value, which will be small in infants less than 2 months old. For tetanic stimulation, 50 Hz is preferable to 20 Hz because at 50 Hz the neuromuscular apparatus is stressed more without much fatigue occurring, as indicated by the greater tetanus : twitch ratios as well as the greater PTF values. Alternating twitch rates of stimulation before the tetanus and afterwards, one can evaluate PTF and the tetanus : twitch ratios. Stimulating at 100 Hz seems not to be of any value, as indicated by the marked-tetanic exhaustion.

Also, to evaluate subtle changes in neuromuscular transmission, we recommend recording neuromuscular events rather than observing them. More prudent decisions are possible, leading to improved patient care.

ACKNOWLEDGEMENTS

The author expresses his sincere gratitude to R. J. Kitz, M.D., J. J. Savarese, M.D. and A. Gissen, M.D. for helping in preparation of the manuscript and Letty Liu, M.D. for her help in collecting the data.

REFERENCES

Ali, H. H., and Savarese, J. J. (1976). Monitoring of neuromuscular function. *Anesthesiology*, **45**, 216.

—— Utting, J. E., and Gray, T. C. (1971). Quantitative assessment of residual antidepolarizing block, Part I. *Br. J. Anaesth.*, **43**, 473.

Brooke, M. H., and Kaiser, K. K. (1970). Muscle fiber types—how many and what kinds? *Arch. Neurol.*, **23**, 369.

Brown, M. D. (1973). Role of activity in the differentiation of slow and fast muscles. *Nature* (*Lond.*), **244**, 178.

Buller, A. J., and Eccles, R. M. (1960). Differentiation of fast and slow muscles in the cat hind limb. *J. Physiol.* (*Lond.*), **150**, 399.

Churchill-Davidson, H. C., and Wise, R. P. (1963). Neuromuscular transmission in the newborn infant. *Anesthesiology*, **24**, 271.

Close, R. (1964). Dynamic properties of fast and slow skeletal muscles of rat during development. *J. Physiol.* (*Lond.*), **173**, 74.

Cook, D. R., and Fischer, C. G. (1978). Characteristics of succinylcholine neuromuscular blockade in neonates. *Anesth. Analg.* (*Cleve.*), **57**, 63.

Curless, R. G. (1977), Developmental patterns of peripheral nerve, myoneural junction and muscle: a review. *Progr. Neurobiol.*, **9**, 197.

Dubowtiz, V. (1968). *Developing and Diseased Muscle*, p. 47. Spastics International Medical Publication and William Heinemann Medical Books Ltd.

Engel, W. K. and Karpati, G. (1968). Impaired skeletal muscle maturation following neonatal neurectomy. *Develop. Biol.*, **17**, 713.

Epstein, R. A., and Epstein, R. M. (1973). The electromyogram and the mechanical response of indirectly stimulated muscle in anesthetized man following curarization. *Anesthesiology*, **38**, 212.

Gatev, V., Stamatova, L., Angelova, B., and Ivanov, I. (1975). Effects of repetitive stimulation on the electrical and mechanical activities of muscles in normal children. *Electromyogr. Clin. Neurophysiol.*, **15**, 339.

Goudsouzian, N. G., Donlon, J. V., Savarese, J. J., and Ryan, D. F. (1975). Reevaluation of dosage and duration of action of d-tubocurarine in the pediatric age group. *Anesthesiology*, **43**, 416.

—— Liu, L., and Savarese, J. J. (1978). Metocurine in infants and children. *Anesthesiology*, **49**, 266.

Katz, R. L. (1973). Electromyographic and mechanical effects of suxamethonium and tubocurarine on twitch: tetanic and post-tetanic responses. *Br. J. Anaesth.*, **45**, 849.

Keens, T. G., Bryan, A. C., Levison, H., and Iannuzo, C. P. (1978). Developmental pattern of muscle fiber types in human ventilatory muscles. *J. Appl. Physiol.*, **44**, 909.

Kelly, S. S., and Roberts, D. V. (1977). The effect of age on the safety factor in neuromuscular transmission in the isolated diaphragm of the rat. *Br. J. Anaesth.*, **149**, 217.

Koenigsberger, M. R., Patten, B., and Lovelace, R. E. (1973). Studies of neuromuscular function in the newborn. I: A comparison of myoneural function in the full term and the premature infant. *Neuropadriatrie*, **4**, 350.

Standaert, F. G. (1964). The mechanism of post-tetanic facilitation in the cat soleus and gastrocnemius muscles. *J. Gen. Physiol.*, **47**, 987.

Stanec, A., Heyduc, J., Stanec, G., and Orkim, L. R. (1978). Tetanic fade and post-tetanic tension in the absence of neuromuscular blocking agents in anesthetized man. *Anesth. Analg.* (*Cleve.*), **57**, 102.

EVOLUTION DE LA TRANSMISSION NEUROMUSCULAIRE CHEZ LE BEBE

RESUME

On a étudié sur 37 bébés et enfants anesthésiés à l'halothane les paramètres cliniques de la transmission neuromusculaire relative à la tension de crispation, la série de quatre et le tétanos. La durée de la contraction a été plus lente chez les bébés âgés de moins d'un mois que chez leurs congénères plus âgés. Ceci peut indiquer une transformation possible des muscles de types lents en muscles de types plus rapides. La série de quatre a atteint 100% dans la plupart des bébés âgés de plus de 2 mois. Pour l'action post-tétanique et les rapports tétanos: crispation ont été nettement plus importants chez les bébés âgés de plus de 2 mois que chez ceux âgés de moins d'un mois. L'épuisement post-tétanique a été constaté sur tous les bébés et enfants après stimulation à 100 Hz. Les rapports tétanos : crispation ont été plus forts chez les bébés de plus de 2 mois et chez les enfants, et la force tétanique a été plus fortement marquée à 50 Hz qu'à 20 Hz. Les données indiquent que l'évolution de la transmission neuromusculaire chez les bébés se produit aux environs du deuxiéme mois.

REIFUNG DER NEUROMUSKULÄREN ÜBERTRAGUNG BEIM KIND

ZUSAMMENFASSUNG

Zuckungsspannung, Viererreihen und Tetanus sowie klinische Bereich neuromuskulären Übertragung wurden bei 37 mit Halothan narkotisierten Kindern und Kleinkindern untersucht. Die Kontraktionen waren langsamer bei Kindern unter einem Monat, verglichen mit den älteren Kindern. Dies konnte eine mögliche Verwandlung langsamer in schnellere Muskeltypen andeuten. Die Viererreihe erreichte bei den meisten Kindern über 2 Monate 100%. Die posttetanische Erleichterung und die Tetanus : Zuckungsverhältnisse waren bei Kindern uber 2 Monate wesentlich grösser als bei solchen unter einem Monat. Posttetanische Etschöpfung ergab sich bei allen Kindern nach Stimulierung bei 100 Hz. Tetanus : Zuckungsverhaltnisse waren grösser bei Kindern über 2 Monaten, und die tetanische Kraft war deutlicher bei 50 Hz als bei 20 Hz. Die Angaben zeigen, dass die Reifung der neuromuskulären Übertragung bei Kleinkindern rund um die beiden ersten Lebensmonate erfolgt.

MADURACION DE LA TRANSMISION NEUROMUSCULAR EN EL BEBE

SUMARIO

Se estudiaron los parámetros clínicos de la tensión contraccional, de serie-de-cuatro y de tétanos en cuanto a la transmisión neuromuscular en 37 bebés y niños anestesiados con halotano. El tiempo de contracción fue más lento en los bebés de menos de 1 mes en comparación con sus contrapartes mayores. Esto puede indicar una posible transformación de los tipos de músculo de lento a más rápido. La serie-de-cuatro alcanzó un 100% en la mayoría de los bebés de más de 2 meses. Las relaciones de facilitación post-tetánica y del tétanos: contracción fueron significativamente mayores en niños de más de 2 meses en comparación con bebés de menos de 1 mes. Se registró una exinanición post-tetánica en todos los bebés y niños después de una excitación a 100 Hz. Las relaciones tétanos: contracción fueron mayores en los bebés de más de 2 meses y en niños y la fuerza tetánica fue más marcada a 50 Hz que a 20 Hz. Los datos indican que la maduración de la transmisión neuromuscular ocurre en bebés en los dos primeros meses o alrededor de esa edad.

Br. J. Anaesth. (1980), **52**, 215

POSTOPERATIVE MUSCLE PAINS AND SUXAMETHONIUM

J. B. BRODSKY AND J. EHRENWERTH

SUMMARY

Two matched groups of patients with Hodgkin's disease undergoing a staging laparotomy received thiopentone, pancuronium bromide or suxamethonium 1.0 mg kg^{-1} (group 2) to facilitate tracheal intubation. There were no differences in the sites or degree of postoperative myalgia between the groups. It is concluded that efforts to reduce the frequency of suxamethonium muscle pains in patients having major abdominal operations are not justified.

Muscle pains following suxamethonium were first noted in 1952 (Bourne, Collier and Somers, 1952). Numerous studies have since confirmed that these myalgias frequently follow minor surgical procedures (Churchill-Davidson, 1954; White, 1962; Craig, 1964; Glauber, 1966), but there is less evidence for their occurrence after major surgery. We studied the occurrence and severity of postoperative muscle pains after a standard abdominal operation to determine if there was any association between myalgia after operation and the use of suxamethonium during operation.

METHODS

Forty consecutive patients with Hodgkin's disease undergoing "staging laparotomy" (splenectomy, liver biopsy, abdominal and pelvic lymph node biopsy, and bone marrow aspiration) were randomly assigned to one of two study groups. Premedication consisted of an opiate and an anticholinergic drug and no patient received diazepam. In the operating theatre, an i.v. cannula was placed in the right hand. Following preoxygenation, anaesthesia was induced in both groups with i.v. thiopentone 4 mg kg^{-1}. Patients in group 1 were then given i.v. pancuronium bromide 0.1 mg kg^{-1}, and tracheal intubation was was performed 3.5–5 min later. Group 2 patients were given i.v. suxamethonium 1.0 mg kg^{-1} and intubation was performed after 45–60 s. No patient in either group received suxamethonium at any other time during the operation. Anaesthesia was maintained with 1.0–2.5% enflurane in 60% nitrous oxide in oxygen in half the number of patients in both groups. In the other patients, anaesthesia was maintained with 70% nitrous oxide in oxygen, supplemented with pethidine. Patients in both groups received pancuronium bromide for muscle relaxation during surgery, and ventilation of the lungs was controlled mechanically.

The occurrence of muscle fasciculations and the degree of relaxation at the time of intubation were noted. Each patient was visited on the 1st and 2nd days after operation by an anaesthetist who was unaware of the drugs received. Standard questions were asked (Churchill-Davidson, 1954), including "Do you have, or have you had any pains in your muscles following your operation?" If the answer was "yes", the location, duration and degree of pain were recorded.

RESULTS

Age, body weight and sex distribution, anaesthetic technique, patient position and duration of surgery were similar in the two groups. All but one patient in group 2 exhibited muscle fasciculations after receiving suxamethonium; no patient in group 1 fasciculated. Relaxation for intubation was considered adequate in all the patients. Seven patients in group 1 (35%) and six in group 2 (30%) experienced myalgia after operation (table I). One patient in group 1 (5%) and one in group 2 (5%) had muscle pains at several sites, but only one patient in the whole series had severe muscle pain at a site different from the operative wound. Complaints of myalgia were as frequent in males as in females. The sites of myalgia were similar to those previously reported following suxamethonium (Burtles and Tunstall, 1961; Craig, 1964). When surgery lasted more than 90 min, 50% of patients experienced muscle pain, compared with a very small frequency of myalgia when surgery lasted less than 90 min (table II).

All patients received opiate analgesic drugs to relieve incisional pain and all were ambulant within

---

JAY B. BRODSKY, M.D.; JAN EHRENWERTH, M.D.; Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305, U.S.A.

0007-0912/80/020215-04 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Patients with postoperative myalgia. Fasciculations: 0 = none visible; 1 = fine facial and/or fingertip; 2 = minimal, trunk and/or extremities: 3 = vigorous trunk or extremities. Relaxation: 0 = inadequate; 1 = vigorous coughing; 2 = slight movement: 3 = complete. Myalgias: 0 = none; 1 = transient; 2 = multiple sites and/or severe single site; 3 = incapacitating*

Age (yr)	Sex	Fasciculations	Relaxation	Myalgia Day 1	Myalgia Day 2	Sites	Duration of surgery (min)
Group 1: Pancuronium							
15	M	0	3	1	0	Backache	105
19	F	0	3	0	1	(L) Shoulder	120
38	M	0	2	0	1	Flank	165
47	F	0	3	0	1	Backache	120
22	F	0	2	2	1	Neck	70
22	F	0	2	1	0	(L) Shoulder	165
31	M	0	3	0	2	Shoulders	110
Group 2: Suxamethonium							
48	F	2	3	1	1	Flank	100
56	M	3	2	1	2	Backache, ankle	120
20	F	3	2	0	1	Backache	105
33	M	3	3	0	1	Backache	120
36	M	3	3	1	0	(L) Shoulder	105
34	M	3	3	0	1	(L) Shoulder	95

TABLE II. *Postoperative myalgia and duration of surgery in group 1 (pancuronium) and group 2 (suxamethonium)*

	Duration of surgery (min)			
	Group 1		Group 2	
	⩽90	>90	⩽90	>90
Myalgias	1	6	0	6
No myalgia	7	6	8	6

24 h after surgery. There were no complications after operation in any patient.

DISCUSSION

In matched patients undergoing a standard abdominal operation we could not demonstrate a difference in the frequency or severity of postoperative myalgia between patients receiving only pancuronium for tracheal intubation and those receiving suxamethonium. Postoperative muscle pain occurs in 0.2–89% of patients who have received suxamethonium (Dottori, Lõf and Ygge, 1965). The wide variation in the reported frequency of suxamethonium myalgia makes it difficult to compare previous studies, since these investigations lacked standardization of the many factors believed to influence muscle pains after operation, such as age, sex, anaesthetic technique, duration and type of surgical procedure, patient position during operation, postoperative care, medication and time and extent of ambulation. Our two groups were identically matched for all of the above and all operations were performed by the same surgical team.

Previous studies have shown that the occurrence of suxamethonium myalgia is greatest after outpatient (Churchill-Davidson, 1954), dental (Glauber, 1966) or other "minor" procedures (Craig, 1964; Dottori, Lõf and Ygge, 1965). The postoperative muscle pains following these minor procedures are probably truly associated with suxamethonium, since they can be modified by a variety of techniques, including pretreatment with a small dose of non-depolarizing myoneural blocking drug before giving suxamethonium (Churchill-Davidson, 1954; Lamoreaux and Urbach, 1960; White, 1962; Dottori, Lõf and Ygge, 1965; Glauber, 1966), lignocaine (Usubiaga et al., 1967; Haldia, Chatterji and Kackar, 1973), thiopentone (Burtles and Tunstall, 1961; Craig, 1964), vitamin C (Gupte and Savant, 1971) and diazepam (Verma, Chatterji and Mathur, 1978). The most commonly employed method, pretreatment with a non-depolarizing myoneural blocker, did not reduce the frequency of myalgia after operation in two well-controlled studies of patients undergoing major abdominal surgery (Bryson and Ormston, 1962; Brodsky, Brock-Utne and Samuels, 1979).

Is suxamethonium myalgia after abdominal surgery a true clinical entity? There were no differences between the patients receiving only pancuronium and those receiving suxamethonium in our study. The presence of fasciculations was not related to the occurrence of muscle pains after operation in this or in previous studies (Lamoreaux and Urbach, 1960; Brodsky and Brock-Utne, 1979).

There are many causes of non-incisional muscle pain after operation. The nature of the surgery determines the time for which the patient is confined to bed after operation. The more active the patient following surgery, the more likely is the occurrence of myalgia (Churchill-Davidson, 1954), and after abdominal surgery patients are not very active. Postoperative wound pain may distract the patient's attention from any relatively minor myalgia. More extensive procedures with greater incisional pain require treatment with potent analgesics and this, in turn, may modify any suxamethonium myalgia. All our patients received morphine or pethidine during the period of study. Endotracheal intubation may cause neck pain and stiffness even when no suxamethonium has been used (Burtles and Tunstall, 1961; Bryson and Ormston, 1962). Duration of surgery and patient position during operation are also factors to be considered. In our study, only one patient of 16 (6%) from both groups in which surgery lasted less than 90 min had muscle pain after operation. Twelve of 24 patients (50%) in whom surgery lasted more than 90 min had postoperative myalgia and there was no difference in the frequency between the two groups (table II). When shoulder pain occurred after operation, it was usually present only in the left shoulder. This may be related to surgical manipulation and retraction in the area of the left diaphragm during splenectomy.

It is not possible to separate true suxamethonium myalgia from muscle pains as a result of other factors. Whatever the cause, only one patient in this study experienced clinically significant non-incisional muscle pain. Therefore we question the need for drug pretreatment for the prevention of suxamethonium myalgia in patients undergoing major abdominal surgery.

ACKNOWLEDGEMENTS

The authors wish to thank Dr Thomas S. Nelsen, Professor of Surgery and Dr Stanley I. Samuels, Assistant Professor of Anesthesia, Stanford University of Medicine, for their co-operation during this study.

REFERENCES

Bourne, J. G., Collier, H. O. J., and Somers, C. F. (1952). Succinylcholine, a muscle relaxant of short action. *Lancet*, **1**, 1225.

Brodsky, J. B., and Brock-Utne, J. G. (1979). Does "self-taming" with succinylcholine prevent postoperative myalgias? *Anesthesiology*, **50**, 265.

—— —— Samuels, S. I. (1979). Pancuronium pretreatment and post-succinylcholine myalgias. *Anesthesiology*, **51**, 259.

Bryson, T. H. L., and Ormston, T. O. G. (1962). Muscle pains following the use of suxamethonium in Caesarean section. *Br. J. Anaesth.*, **34**, 476.

Burtles, R., and Tunstall, M. E. (1961). Suxamethonium chloride and muscle pains. *Br. J. Anaesth.*, **33**, 24.

Churchill-Davidson, H. C. (1954). Suxamethonium (succinylcholine) chloride and muscle pains. *Br. Med. J.*, **1**, 74.

Craig, H. J. L. (1964). The protective effect of thiopentone against muscular pain and stiffness which follows the use of suxamethonium chloride. *Br. J. Anaesth.*, **36**, 612.

Dottori, O., Lof, B. A., and Ygge, H. (1965). Muscle pains after suxamethonium. *Acta Anaesthesiol. Scand.*, **9**, 247.

Glauber, D. (1966). The incidence and severity of muscle pains after suxamethonium when preceded by gallamine. *Br. J. Anaesth.*, **38**, 541.

Gupte, S. R., and Savant, N. S. (1971). Post suxamethonium pains and vitamin C. *Anaesthesia*, **26**, 436.

Haldia, K. N., Chatterji, S., and Kacker, S. N. (1973). Intravenous lignocaine for prevention of muscle pain after succinylcholine. *Anesth. Analg.* (*Cleve.*), **52**, 849.

Lamoreaux, L. F., and Urbach, K. F. (1960). Incidence and prevention of muscle pain following the administration of succinylcholine. *Anesthesiology*, **21**, 394.

Usubiaga, J. E., Wikinski, J. A., Usubiaga, L. E., and Molina, F. (1967). Intravenous lidocaine in the prevention of postoperative muscle pain caused by succinylcholine administration. *Anesth. Analg.* (*Cleve.*), **46**, 225.

Verma, R. S., Chatterji, S., and Mathur, N. (1978). Diazepam and succinylcholine-induced muscle pains. *Anesth. Analg.* (*Cleve.*), **57**, 295.

White, D. C. (1962). Observations on the prevention of muscle pains after suxamethonium. *Br. J. Anaesth.*, **34**, 332.

DOULEURS MUSCULAIRES POSTOPERATOIRES ET LE SUXAMETHONIUM

RESUME

Pour faciliter l'intubation trachéale, on a administré à deux groupes de malades assortis souffrant de la maladie de Hodgkin et devant subir une laparotomie en plusieurs temps, du thiopentone, du bromure de pancuronium ou du suxaméthonium à raison de 1 mg kg^{-1} (groupe 2). Il n'y a eu aucune différence dans les emplacements ou le degré de myalgie postopératoire entre les groupes. On en a conclu que les efforts faits pour diminuer la fréquence des douleurs musculaires provoquées par le suxaméthonium, chez les malades subissant des interventions abdominales majeures, ne sont pas justifiés.

POSTOPERATIVE MUSKELSCHMERZEN UND SUXAMETHONIUM

ZUSAMMENFASSUNG

Zwei abgestimmte Gruppen von Patienten mit Lymphgranulomen wurden einer Lapatoromie unterzogen und

erhielten Thiopenton, Pancuroniumbromid oder Suxamethonium 1,0 mg kg^{-1} (Gruppe 2) zur Erleichterung einer Trachealröhreneinführung. Es gab keine Unterschiede in den Stellen oder im Ausmass der postoperativen Myalgie zwischen den beiden Gruppen. Daraus wird geschlossen, dass Bemühungen, die Häufigkeit von durch Suxamethonium bewirkten Muskelschmerzen zu reduzieren—bei Patienten mit grösseren Unterleibsoperationen—nicht gerechtfertigt sind.

DOLORES MUSCULARES POSTOPERATORIOS Y SUXAMETONIO

SUMARIO

Se administró a dos grupos emparejados de pacientes con enfermedad de Hodgkin sometidos a una laparotomia en fases 1,0 mg kg^{-1} de tiopentona, bromuro de pancuronio o sexametonio (grupo 2) con el objeto de facilitar la intubación tranqueal. No hubo diferencia alguna en el lugar o el grado de las mialgias postoperatorias entre los dos grupos. Se concluye que los esfuerzos para reducir la frecuencia de los dolores musculares debidos al suxametonio en pacientes sometidos a operaciones abdominales mayores no se justifican.

Br. J. Anaesth. (1980), **52**, 219

ENFLURANE IN OUTPATIENT PAEDIATRIC DENTAL ANAESTHESIA

A comparison with halothane

R. H. A. HOYAL, C. PRYS-ROBERTS AND P. J. SIMPSON

SUMMARY

Enflurane and halothane were compared as volatile supplements to nitrous oxide anaesthesia for 80 children presenting for outpatient dental extractions. Induction and maintenance of anaesthesia were comparable and satisfactory with both agents, but recovery of consciousness was significantly quicker following enflurane anaesthesia. Full recovery from either enflurane or halothane was of similar duration.

For many years halothane has been the volatile agent which has been used most frequently for outpatient dental anaesthesia. Certain physical properties of enflurane, notably its low solubility in blood and tissues and its low level of biotransformation (Chase et al., 1971; Cohen, 1971), have made the agent a potentially attractive alternative to halothane as a supplement to nitrous oxide in outpatient anaesthesia (Steward, 1977; Davidson, 1978). Since no previous comparison of enflurane and halothane in outpatient dental anaesthesia had been described, we compared these agents as volatile supplements to nitrous oxide and oxygen in children presenting for dental extractions at the Bristol Dental Hospital.

METHODS

Eighty children aged between 5 and 12 yr, requiring extraction of two to six teeth (in order to standardize both the quality and duration of anaesthesia) were allocated randomly to one of two equal groups, one receiving enflurane and the other halothane. Children giving a history of epilepsy or renal disease were excluded. None of the children received premedication. Induction was undertaken in the supine position with a nasal mask, using a continuous flow Bain circuit and active scavenging to avoid pollution in the theatre. Nitrous oxide 8 litre min^{-1} and oxygen 3 litre min^{-1} were administered for 45 s and the concentrations were then adjusted to 6 litre min^{-1} and 2 litre min^{-1} respectively and equipotent concentrations, based on the published MAC values of enflurane (Gion and Saidman, 1971) or halothane, were added, the concentration of either agent being increased at intervals of four breaths. The consultant administering the anaesthesia was not aware as to whether he was administering halothane or enflurane, the control of the relevant vaporizer being adjusted by one of the authors (R. H. A. H.). The concentration of enflurane was increased in steps of 1 vol % to a maximum of 5 vol % and that of halothane in 0.5-vol % steps to a maximum of 2.5 vol %. These maximum concentrations were maintained until induction was considered complete as judged by adequate jaw relaxation. At this point surgery began and the maintenance concentrations of enflurane or halothane were decreased to 2.0 and 1.0 vol % respectively. Administration of the volatile agent and nitrous oxide was discontinued following removal of the oral prop at the end of surgery and oxygen 100 vol % was administered for about 30 s. Enflurane was vaporized using an Enfluratec (Cyprane Ltd, Keighley) and halothane using a Fluotec Mark III (Cyprane Ltd) mounted in a "Selectatec" quick-release mount. Both vaporizers were calibrated by interferometry (Riken Type 17).

Induction time was defined as the time from the introduction of the volatile agent to the time when eyeball movement had ceased and the patient's jaw was relaxed sufficiently to permit the insertion of a V-pack (Vickery and Burton, 1977). The time to the loss of eyelash reflex was noted also, as was the frequency of complications such as hiccup, breath-holding and stridor during the induction period. The recovery times were recorded by a small group of experienced recovery nurses, who were not told which agent had been used, and were measured from

---

R. H. A. HOYAL,* B.SC., M.B., B.S., F.F.A.R.C.S.; C. PRYS-ROBERTS, M.A., D.M., PH.D., F.F.A.R.C.S.; P. J. SIMPSON, M.D., F.F.A.R.C.S.; Department of Anaesthetics, University of Bristol, Royal Infirmary, Bristol.

* Present address: Wycombe General Hospital, High Wycombe, Bucks.

0007-0912/80/020219-04 $01.00

© Macmillan Journals Ltd 1980

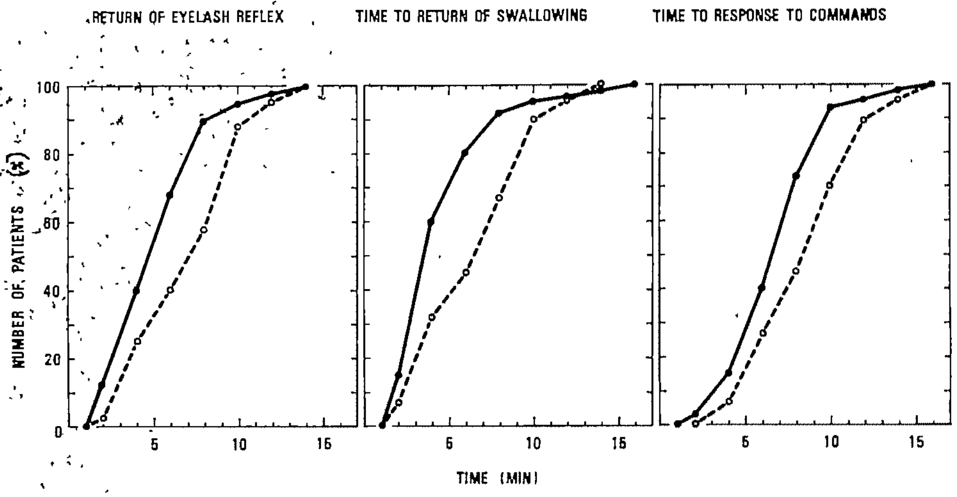


FIG. 1.-Cumulative frequencies of early recovery times following enflurane (●——●) and halothane (○- - - ○) in two groups of 40 children.

the time at which surgery was completed and oxygen 100 vol % introduced to the following stages of recovery: the return of the eyelash reflex, the return of swallowing, the ability to respond to commands, the ability to stand with the eyes closed without swaying and the ability to walk a straight line. These last two criteria were considered to represent full recovery. All measurements were made to the nearest 6 s.

Statistical evaluation of the results was based on unpaired Student's *t* tests. A questionnaire asking about the child's activities after returning home was given to each accompanying parent or guardian. This enquired about the frequency of headache, dizziness, nausea, vomiting, muscle pains and bad dreams. The delays in returning to a normal appetite and to normal activity were noted. Statistical evaluation of these data was based on the χ^2 test.

RESULTS

Both agents were accepted readily by the children and in the majority induction was smooth and free from complications. The mean time to loss of eyelash reflex was 2.1 min (SD 0.9) for enflurane and 2.0 min (SD 1.3) for halothane. Mean induction times were 4.2 min (SD 1.4) for enflurane and 4.1 min (SD 1.7) for halothane. These differences were not statistically significant. In the group receiving enflurane, induction was complicated by hiccup in five patients, breath-holding in two patients and stridor in one patient, whereas in the group receiving halothane, induction was complicated by breath-holding in only two patients.

Maintenance of anaesthesia after insertion of the V-pack was uncomplicated in all children and there was no significant difference between the mean

TABLE I. *Immediate post-anaesthetic complications. Differences between enflurane and halothane groups were not statistically significant by χ^2 test*

	Enflurane	Halothane
Crying	21	18
Vomiting	5	6
Slight hypertonia	3	2

TABLE II. *Late post-anaesthetic complications. Results of first 32 returned questionnaires in each group. Differences between enflurane and halothane groups were not statistically significant by χ^2 test*

	Enflurane			Halothane		
Headache	10			7		
Dizziness	9			10		
Nausea	10			11		
Vomiting	9			8		
Muscle pains	1			4		
Bad dreams	1			4		
	Same day	Next day	Later	Same day	Next day	Later
Return of normal appetite	20	11	1	26	5	1
Return of normal activity	20	11	1	20	9	3

duration of surgery in the enflurane (4.4 min, SD 2.6) or halothane (3.5 min, SD 3.0) groups nor between the total anaesthetic times for the enflurane (8.6 min, SD 2.9) or halothane (7.5 min, SD 3.4) groups. During the early recovery period, the group which received enflurane had a shorter mean recovery time (fig. 1) than the halothane group, as measured by the return of the eyelash reflex and the return of swallowing. In each case the differences were statistically significant ($P<0.01$). The ability to respond to command occurred earlier with enflurane and this difference was statistically significant ($P<0.05$).

The late recovery times, as measured by the ability to stand without swaying with the eyes closed, were shorter following enflurane anaesthesia (19 min, SD 7) compared with the halothane group (22 min, SD 7), but this difference was not statistically significant. The ability to walk in a straight line was not significantly shorter in the enflurane group (24 min, SD 8) compared with the halothane group (27 min, SD 8). The immediate post-anaesthetic complications are listed in table I. Examination of the first 32 completed questionnaires returned from each group (table II) showed only minor differences between the groups with regard to late post-anaesthetic complications and the return to a normal appetite and activity.

DISCUSSION

Under the conditions of this study there was little to choose between enflurane and halothane, since both agents provided equally satisfactory induction of anaesthesia and the quality of surgical anaesthesia was similar with the two agents. Enflurane was accepted readily by the children, and apart from occasional bouts of hiccup, which did not seriously interrupt the induction sequence, the induction of anaesthesia was smooth and uncomplicated. Despite the lower solubility of enflurane in blood, the times to loss of consciousness and to full surgical anaesthesia were similar to those for halothane. The early recovery from enflurane anaesthesia was significantly faster than that in the group who received halothane, but this advantage was not supported by a comparable difference in the late recovery times. Thus both groups of children were ready to leave the recovery area after about 25 min.

It is difficult to make direct comparisons between our results and those of Steward (1977) or Davidson (1978). Steward induced anaesthesia with i.v. thiopentone, and there was no attempt to use specific equipotent anaesthetic concentrations of the anaesthetic agents in Davidson's study. Some of the patients in the study by Govaerts and Sanders (1975) and that of Davidson received premedication. In contrast to these studies, we could not demonstrate a significantly shorter full recovery time and this may simply reflect the need for longer periods of anaesthetic administration to differentiate between the differences in the physical characteristics of the two agents.

We conclude, therefore, that enflurane can be considered as an acceptable but expensive alternative to halothane in outpatient paediatric dental practice.

ACKNOWLEDGEMENTS

We wish to thank the anaesthetic nursing staff of the Bristol Dental Hospital for their co-operation in the conduct of this study and also the surgical dental staff whose patients we studied.

REFERENCES

Chase, R. E., Holaday, D. A., Fiserova-Bergerova, V., Saidman, L. J., and Mack, F. E. (1971). The biotransformation of Ethrane in man. *Anesthesiology*, **35**, 262.

Cohen, E. N. (1971). Metabolism of the volatile anesthetics. *Anesthesiology*, **35**, 262.

Davidson, S. H. (1978). A comparative study of halothane and enflurane in paediatric outpatient anaesthesia. *Acta Anaesthesiol. Scand.*, **22**, 58.

Gion, H., and Saidman, L. J. (1971). The mean alveolar concentration of enflurane in man. *Anesthesiology*, **35**, 361.

Govaerts, M. J. M., and Sanders, M. (1975). Induction and recovery with enflurane and halothane in paediatric anaesthesia. *Br. J. Anaesth.*, **47**, 877.

Steward, D. J. (1977). A trial of enflurane for paediatric outpatient anaesthesia. *Can. Anaesth. Soc. J.*, **24**, 603.

Vickery, I. M., and Burton, G. W. (1977). Throat packs for surgery. *Anaesthesia*, **32**, 565.

L'ENFLURANE POUR L'ANESTHESIE PEDIATRIQUE DENTAIRE SUR DES PATIENTS DE CONSULTATION EXTERNE

Comparaison avec l'halothane

RESUME

On a comparé l'enflurane et l'halothane en tant que suppléments volatils pour l'anesthésie au protoxyde d'azote sur 80 enfants se présentant en tant que patients de consultation externe pour des extractions dentaires. L'induction et le maintien de l'anesthésie ont été comparables et satisfaisants avec ces deux agents, mais la reprise de conscience a été sensiblement plus rapide après l'anesthésie à l'enflurane. La récupération complète, qu'il s'agisse de l'enflurane ou de l'halothane, a été d'une durée similaire.

ENFLURAN FÜR ZAHNNARKOSE BEI AMBULANT BEHANDELTEN KINDERN

Ein Vergleich mit Halothan

ZUSAMMENFASSUNG

Enfluran und Halothan wurden als ätherische Zusätze zu Stickoxydnarkose bei 80 Kindern verglichen, bei denen ambulant Zahnextraktionen vorgenommen wurden. Einleitung und Erhaltung der Narkose war bei beiden Mitteln vergleichbar und zufriedenstellend, aber die Widererlangung des Bewusstseins war mit Enfluran wesentlich schneller. Vollständige Erholung von der Narkose dauerte bei beiden Mitteln gleich lang.

ENFLURANO EN LA ANESTESIA DENTAL PEDIATRICA DE PACIENTES EXTERNOS

Una comparación con halotano

SUMARIO

Se llevó a cabo la comparación del enflurano con el halotano como suplementos volatiles al óxido nitroso para la anestesia de 80 niños que se sometían a extracciones dentales como pacientes externos. La inducción y la mantención de la anestesia fueron comparables y satisfactorias con ambos agentes, pero la recuperación del sentido fue mucho más rapido con la anestesia por enflurano. La recuperación total con el enflurano o el halotano tuvo una duración similar.

Br. J. Anaesth. (1980), **52**, 223

ADVERSE EFFECTS OF BUFFERED GLUTARALDEHYDE ON THE HEIDBRINK EXPIRATORY VALVE

S. M. Mostafa

SUMMARY

The effect of chemical disinfection of the Heidbrink expiratory valve in buffered glutaraldehyde (Cidex solution) was investigated. Cidex caused stickiness and increased the opening pressure and resistance of the valve to different gas flow rates. An electrolytic type of corrosion may also have occurred. However, autoclaving of the Heidbrink valve did not appear to cause corrosion or significant alteration of its opening pressure or resistance.

The use and efficiency of buffered glutaraldehyde (Cidex) as a chemical disinfectant for anaesthetic equipment have been described by Haselhuhn, Broson and Borick (1967), Meeks, Pembleton and Hench (1967) and Stark (1972). Residual air, wetness and the need for rinsing and packaging after disinfection are among the disadvantages of chemical disinfection described by Lumley (1976). Apart from absorption by rubber and plastics (Varpela, Otterström and Hackman, 1971), Cidex was reported to be non-corrosive to metals and harmless to anaesthetic equipment. It was observed in our hospital that, despite the Heidbrink valves (Mushin and Mapleson, 1954) being adjusted to the fully open position, many of them were sticking and hissing loudly. As the valves were routinely disinfected in Cidex solution, this investigation was undertaken to determine if this method of disinfection was responsible for the above problem. Changes in the opening pressure and the resistance of each valve to different gas flow rates (expressed as the pressure decreases across the valve) were also measured.

METHOD

Sixteen valves were investigated. Six of these were 2–3 years old and were routinely disinfected in Cidex solution (group I). The other 10 valves were new (group II). These were equally divided into two groups. Following their use during anaesthesia, the new valves of each group were washed thoroughly in water then sterilized either by autoclaving (group III) or by immersion in Cidex solution (group IV). The valves in group IV were further rinsed in water following sterilization in Cidex.

A technique similar to that described by Mushin and Mapleson (1954) was used to measure the opening pressure and resistance of the old valves (group I) to different gas flow rates employing a calibrated oxygen flowmeter and U-tube water manometer, the valves being in the upright position. Naked eye and microscopic examination of each valve disc and pin were performed. The new valves were investigated similarly both before (group II) and 10 months after their use in clinical practice (groups III and IV). Furthermore, the discs of two valves from group I and IV and one valve in group III were also examined under a Stereoscan electron microscope.

RESULTS

The mean opening pressure and resistance for a given gas flow rate for each group of valves are presented in table I. For a given flow rate the mean resistances of the valves in groups I and IV were approximately twice those in groups II and III. In the clinical range of gas flow rate (30 litre min^{-1}) the mean pressures were 0.78, 0.28, 0.28 and 0.66 kPa in groups I, II, III and IV respectively. Similarly, the mean opening pressures of the valves in groups I and IV were greater than those in groups II and III. The values were 0.56, 0.08, 0.10 and 0.28 kPa for groups I, II, III and IV respectively.

Naked eye examination

Group I. The changes in the discs and pins of the valves are typified by valve D (fig. 1). Both surfaces of each disc were dull in appearance. The disc and its pin appeared to be diffusely covered by a thin film of foreign substance. A number of irregular black areas 0.5–2 mm in diameter were present on both surfaces of the disc, particularly near its centre. These were obviously caused by corrosion.

S. M. Mostafa, M.B., CH.B.(CAIRO), M.R.C.S.(ENG.), L.R.C.P.(LONDON), F.F.A.R.C.S.(ENG.), Selly Oak Hospital, Birmingham B29 6JD.

0007–0912/80/020223-05 $01.00

© Macmillan Journals Ltd 1980

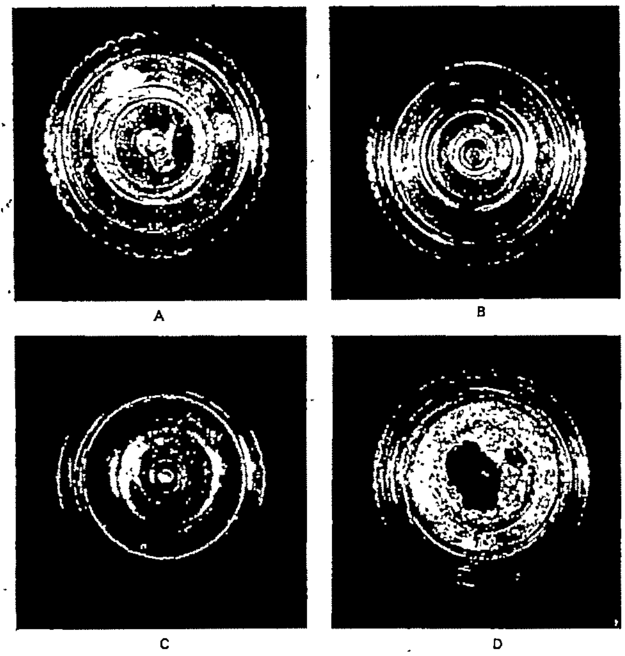


FIG. 1. Four Heidbrink valve discs. DISC A: new valve (group II). Disc B: new valve sterilized by autoclaving (group III). Disc C: new valve disinfected by Cidex (group IV). Disc D: old valve in group I also disinfected by Cidex showing signs of corrosion.

Group II. The disc and pin surfaces of the valves in this group were smooth, bright in appearance and free from cracks or foreign substances (valve A, fig. 1).

Group III. No major differences between the discs and pins of the valves in this group and those in group II were seen (valve B, fig. 1).

Group IV. The discs and pins appeared dull and covered by a substance similar to that found on the discs in group I (valve C, fig. 1), but no black areas in the discs were seen.

Microscopic and Stereoscan electron microscopic examination

Group I. Several aggregated particles of variable size and shape were seen, scattered diffusely on both surfaces of each disc and its pin. Pitting and cracking of the disc surfaces were found (fig. 2).

Groups II and III. The surfaces of the discs and pins of the valves in both groups appeared irregular but smooth and free from pits, cracks or deposits of foreign substance (fig. 3).

Group IV. Particles similar to those found on the discs of the valves in group I were also seen on the discs and pins of the valves in this group. Only a few pits, but no cracks in the disc surfaces were present (fig. 4).

DISCUSSION

In semi-closed systems the resistance to expiration resides in the Heidbrink valves. A high resistance to expiration will eventually lead to an increase in the work of breathing. Nunn (1969) suggested that, at gas flow rate of 30 litre min^{-1} the pressure decrease across the expiratory valve should not exceed 0.29 kPa. The resistance in all the valves in group I at that flow rate exceeded this value (table I). Furthermore, the mean resistance of the valves in group IV (after 10 months of clinical use) at the same gas flow rate had doubled and exceeded 0.29 kPa. Only a small change was found in resistance of the valves in group III after a similar period of usage.

When rendered alkaline (activated), glutaraldehyde gradually undergoes polymerization and loses it activity. At pH 7.5–8.5, polymerization is slowed down so that full antimicrobial activity is maintained

TABLE I. *Opening pressures and mean resistances of the Heidbrink valves to different gas flow rates (range in parentheses)*

	Mean resistance (kPa)			
Gas flow rate (litre min^{-1})	Group I (6 valves)	Group II (10 valves)	Group III (5 valves)	Group IV (5 valves)
10	0.50 (0.44–0.53)	0.08 (0.05–0.11)	0.12 (0.08–0.14)	0.30 (0.23–0.35)
20	0.62 (0.56–0.66)	0.16 (0.13–0.19)	0.21 (0.17–0.23)	0.48 (0.41–0.53)
30	0.78 (0.72–0.8)	0.28 (0.25–0.29)	0.28 (0.26–0.29)	0.66 (0.57–0.75)
40	0.86 (0.80–0.91)	0.35 (0.32–0.39)	0.36 (0.34–0.39)	0.76 (0.64–0.83)
50	0.95 (0.89–1.01)	0.44 (0.40–0.51)	0.45 (0.42–0.49)	0.89 (0.79–0.95)
60	1.18 (1.12–1.24)	0.55 (0.52–0.6)	0.58 (0.54–0.62)	1.02 (0.90–1.08)
Opening pressure (kPa)	0.56 (0.53–0.62)	0.08 (0.05–0.12)	0.10 (0.07–0.12)	0.28 (0.22–0.32)

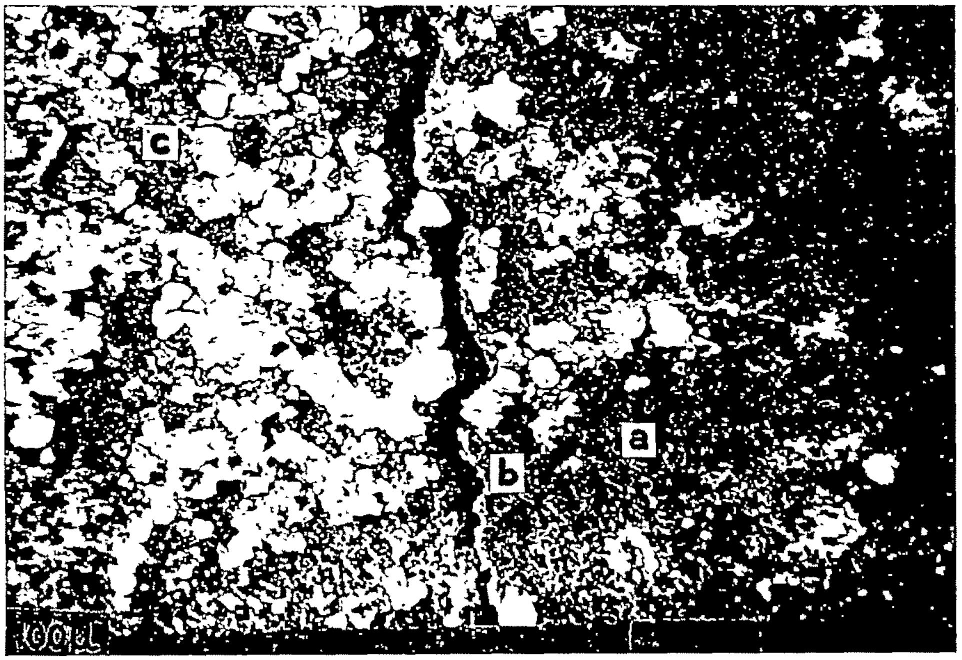


FIG. 2. The inferior surface of a disc from a valve in group I under high magnification (S.E.M.). It shows pitting (a), cracking (b) and aggregated particles on the surface of the disc (c).

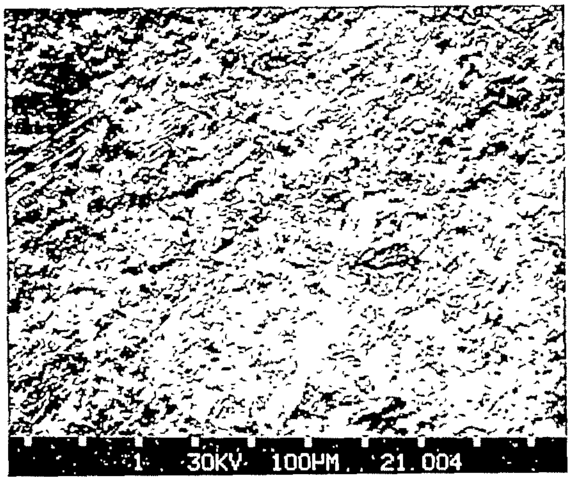


FIG. 3. Inferior surface of a disc from a valve in group III (S.E.M.). The surface of the disc appears to be intact and no foreign particles can be seen.

for at least 2 weeks. Stereoscan electron microscopic examination of the discs showed that a polymer had formed on the surfaces of the discs and the pins of the valves which were sterilized in Cidex solution (figs 2, 4). The formation of glutaraldehyde polymer on the surfaces of the disc, the pin and possibly its guide will reduce the free movement of the pin through its guide and will result in sticky surfaces. This will lead to stickiness and an increase in the opening pressure and resistance of the valves. It has been suggested by the manufacturers that this might result from improper rinsing of the valves following disinfection in Cidex solution. This might have been the case for the old valves (group I), but not for the valves in group IV, since the valves were rinsed meticulously. Presumably, the increased resistance to expiration does not lead to any clinical ill-effect. However, it is reasonable to suggest that such resistance should be controllable and valves used should have a low resistance which can be varied at will.

Glutaraldehyde is non-corrosive, and Cidex solution contains an anti-corrosive agent. However, the discs of the valves in group I showed marked corrosion and the discs in group IV showed early signs of corrosion. The components of the Heidbrink valves are made or plated with dissimilar metals which are in contact most of the time. It is reasonable to assume that the repeated and prolonged immersion of the valves in an electrolyte solution such as Cidex may lead to an electrolytic type of corrosion of the discs of the valves. Also, given time, the valves in group IV would be likely to develop a degree of corrosion similar to that in group I. Stark (1972)

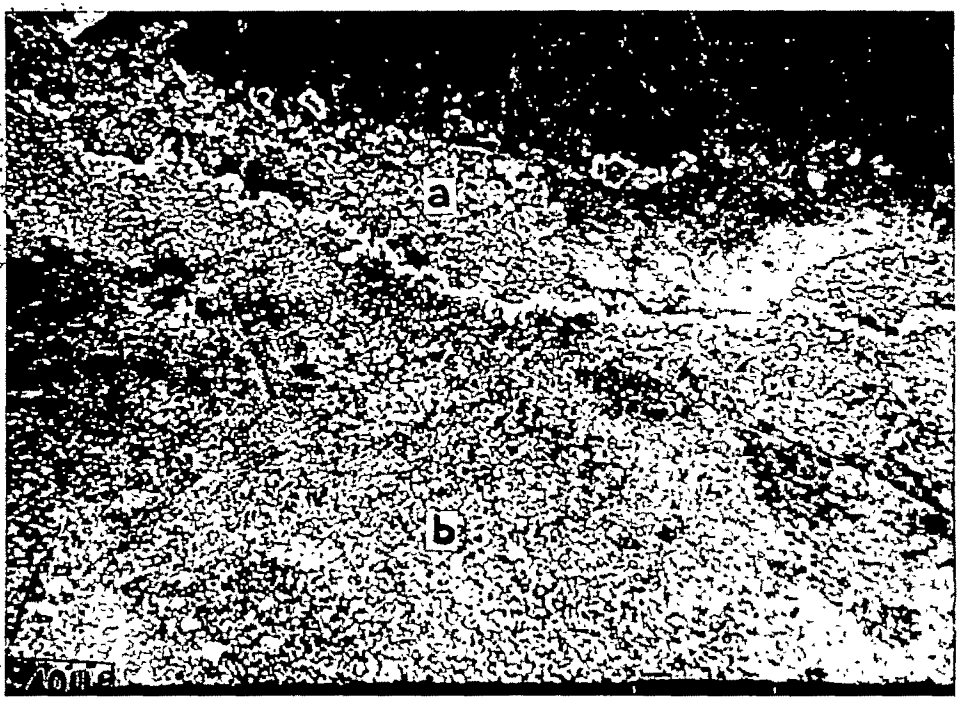


FIG. 4. Inferior surface of a disc from a valve in group IV (S.E.M.). Scattered aggregated particles (a) covering the disc surface and only a few pits can be seen (b). No cracks are visible.

stated that, where a cold sterilizing agent is chosen, glutaraldehyde "used strictly to the manufacturer's instructions is the agent of choice". Therefore, in order to reduce the risk of corrosion and to ensure total elimination of residual air from the valve for efficient disinfection and rinsing, complete dismantling of each Heidbrink valve is necessary. This would be time-consuming and could damage the components of the valve.

In group III stickiness was not a problem and increase in the opening pressure or resistance of the valves was small (table I). Furthermore, there was no corrosion in any valve disc.

These findings suggest that sterilization by autoclaving is more suitable and less harmful to the Heidbrink valves than is Cidex solution.

ACKNOWLEDGEMENTS

I would like to thank Dr D. J. Stratford and Mr P. Done, Department of Physical Metallurgy and Material Science, Birmingham University, for their help and advice during conducting this investigation.

REFERENCES

Haselhuhn, D. H., Broson, F. W., and Borick, P. M. (1967). "In use" study of buffered glutaraldehyde for cold sterilization of anesthesia equipment. *Anesth. Analg. (Cleve.)*, **46**, 468.

Lumley, J. (1976). Decontamination of anaesthetic equipment and ventilators. *Br. J. Anaesth.*, **48**, 3.

Meeks, C. H., Pembleton, W. E., and Hench, M. E. (1967). Sterilization of anesthesia apparatus. *J.A.M.A.*, **199**, 276.

Mushin, W. M., and Mapleson, W. W. (1954). Pressure-flowrate characteristics of expiratory valves. *Br. J. Anaesth.*, **26**, 3.

Nunn, J. F. (1969). *Applied Respiratory Physiology*, 1st edn, p. 83. London: Butterworths.

Stark, D. C. C. (1972). Sterilization by chemical agents. *Int. Anesthesiol. Clin.*, **10**, 49.

Varpela, E., Otterström, S., and Hackman, R. (1971). Liberation of alkalinized glutaraldehyde by respirators after cold sterilization. *Acta Anaesthesiol. Scand.*, **15**, 291.

EFFETS ADVERSES DU GLUTARALDEHYDE TAMPON SUR LA SOUPAPE EXPIRATOIRE D'HEIDBRINK

RESUME

L'effet de la désinfection chimique de la soupape expiratoire d'Heidbrink dans du glutaraldéhyde tampon (solution de Cidex) a fait l'objet de recherches. Le Cidex provoque une certaine viscosité et fait augmenter la pression d'ouverture et la résistance de la soupape aux différents debits de gaz. Il peut aussi se produire un type électrolytique de corrosion. De toute façon, le passage à l'autoclave de la soupape d'Heidbrink ne semble pas entraîner de corrosion ou de modification appréciable de sa pression d'ouverture ou de sa résistance.

SCHÄDLICHE WIRKUNGEN VON GEPUFFERTEM GLUTARALDEHYD AUF DAS HEIDBRINK-AUSATMUNGSVENTIL

ZUSAMMENFASSUNG

Die Wirkung chemischer Desinfektion des Heidbrink-Ausatmungsventils in gepuffertem Glutaraldehyd (Cidex-Losung) wurde untersucht. Cidex verursacht Klebrigkeit und erhöhte den Öffnungsdruck und den Widerstand des Ventils auf verschiedene Gasdurchflussraten. Auch eine elktrolytische Form der Korrosion konnte erfolgt sein. Abkochen des Ventils schien jedoch weder Korrosion noch wesentliche Änderungen seines Offnungsdruckes oder Widerstandes zu bewirken.

EFECTOS CONTRARIOS DEL GLUTARALDEHIDO TAMPON EN LA VALVULA EXPIRATORIA DE HEIDBRINK

SUMARIO

Se averiguó el efecto de la desinfección química de la válvula expiratoria de Heidbrink en glutaraldehido tampón (solución Cidex). El Cidex causó una viscosidad y aumentó la presión y resistencia de apertura de la válvula en distintos ritmos de flujo del gas. También, puede haber ocurrido un tipo de corrosión electrolítica. Sin embargo, la esterilización en autóclave de la válvula de Heidbrink no parece haber causado alguna corrosión ni una alteración significativa de su presión o resistencia de apertura.

Br. J. Anaesth. (1980), **52**, 229P

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

LONDON MEETING

NOVEMBER 23, 1979

FENTANYL BY INFUSION—A METHOD OF TOTAL DOSE REDUCTION

A. G. H. Cole, C. J. Hinds and P. V. Cole
Department of Anaesthesia, St Bartholomew's Hospital, London

Fentanyl is widely employed as an analgesic supplement to nitrous oxide and oxygen anaesthesia. Because of its short duration of action, it may be used in larger doses than any other strong analgesic and it has been noticed that doses of 15–20 $\mu g\ kg^{-1}$ are associated with cardiovascular stability. Even larger doses (50 $\mu g\ kg^{-1}$) are associated with little or no metabolic response to surgery (so-called "stress-free" anaesthesia). However, doses of this magnitude may be associated with respiratory depression after operation.

Because fentanyl is redistributed rapidly it was felt that, if it were administered by continuous infusion, it might be possible to achieve the same effect with a lower total dose. In this way the danger of respiratory depression in the period after operation might be avoided.

Patients undergoing routine lower abdominal gynaecological operations were studied. Following premedication with diazepam 10 mg orally 2 h before operation, anaesthesia was induced with a sleep-dose of thiopentone, muscle relaxation obtained with tubocurarine 0.6 $mg\ kg^{-1}$ and anaesthesia maintained with nitrous oxide and oxygen (2 : 1). Three patients received bolus doses of fentanyl 15 $\mu g\ kg^{-1}$. In the others an infusion of fentanyl was commenced immediately following induction of anaesthesia and continued until approximately 15 min from the end of surgery. Venous blood samples were taken at 5, 10 and 15 min after the bolus dose or the start of the infusion and at 15-min intervals thereafter. In addition, samples were obtained at 5, 10, 15 and 30 min after the cessation of the infusion. Serum fentanyl concentrations were measured in all samples using the radio-immunoassay technique described by Michiels, Hendriks and Heykants (1977).

In the patients who received bolus doses, the serum concentrations compared well with existing work (Schleimer et al., 1976). In the group who received infusions of fentanyl, the first five had an infusion at a steady rate of 0.083 $\mu g\ kg^{-1}\ min^{-1}$ throughout. In these patients, although an adequate plateau serum concentration was achieved (mean = 7.8 $ng\ ml^{-1}$), the rate of increase of serum fentanyl was considered to be too slow. Therefore, in later studies, the infusion rate was doubled for the first 10 min. Using this regime the total dose of fentanyl given at the end of 1 h was 5.3 $\mu g\ kg^{-1}$ (approximately one-third that following a bolus dose). Fifteen minutes after the end of the infusion the mean serum fentanyl concentration was found to be 4.0 $ng\ ml^{-1}$.

All patients remained adequately anaesthetized with a stable cardiovascular system and there was rapid reversal of anaesthesia.

REFERENCES

Michiels, M., Hendriks, R., and Heykants, J. (1977). *Eur. J. Clin. Pharmacol.*, **12**, 153.

Schleimer, R., Benjamini, E., Eisele, J., and Henderson, G. (1976). *Fed. Proc.*, **35**, 346.

EFFECT OF FENTANYL ON REFLEXLY EVOKED CHANGES IN HEART RATE MEDIATED BY THE CARDIOMOTORVAGUS

A. Scott and J. G. Whitwam
Department of Anaesthetics,
Royal Postgraduate Medical School, Du Cane Road, London

Stimulation of somatic nerves of the dog evokes increases in heart rate which are caused by both increased sympathetic activity and inhibition of vagal activity (Norman and Whitwam, 1973; Kumagai, Norman and Whitwam, 1975). The results presented here are an initial attempt to obtain quantitative data concerning the effect of potent analgesic drugs on these responses.

Neuromuscular blockade was induced in eight dogs anaesthetized with methohexitone 5–8 $mg\ kg^{-1}$ followed by chloralose 20 $mg\ kg^{-1}\ h^{-1}$ with suxamethonium 1–2 $mg\ kg^{-1}\ h^{-1}$ and the lungs were ventilated artificially. Systemic arterial pressure and heart rate were recorded. Trains of supramaximal stimuli (100 V, 0.5 ms, 30 Hz) were applied from a stimulator (Grass S88) using bipolar silver–silver chloride electrodes to a desheathed portion of the lateral cutaneous branch of the radial nerve, exposed in the foreleg, immersed in mineral oil and cut distally. Efferent activity in sympathetic nerves was blocked with bretylium tosylate 10 $mg\ kg^{-1}$.

The resting heart rate and arterial pressure were 75.4 ± 17.7 (SD) beat min^{-1} and 164 ± 23.6 mm Hg. Trains of stimuli applied to the radial nerve caused an average maximum increase in heart rate of 66.9 ± 15.2 beat min^{-1}. Fentanyl 50 $\mu g\ kg^{-1}$ i.v. caused a reduction in resting heart rate to 47 ± 8.5 beat min^{-1} and arterial pressure to 113 ± 28.5 mm Hg. Thereafter the average maximum change in heart rate at 5, 10, 30 and 45 min respectively was reduced by 31.6%, 32.6%, 22.3% and 16.3% of its control value before fentanyl. Moreover, fentanyl produced a marked change in the pattern of the evoked response characterized by an early peak and rapid fall-off during stimulation. The pattern of response also differed during an infusion of nitroprusside, sufficient to cause a decrease in resting arterial pressure, when the maximum increase in the evoked heart rate response occurred at the end of the period of stimulation.

Following the first observation period a further 50–70 μg kg^{-1} of fentanyl reduced the evoked responses to 26% of the control value. Naloxone 2 mg i.v. restored arterial pressure, heart rate and evoked responses to greater than control values.

This study demonstrated that fentanyl causes increased activity of the baroreflexes, confirming the work of Laubie and others (1974). It also showed that, in the dog, fentanyl 50 μg kg^{-1} reduces reflexly evoked heart rate responses by only about one-third, and the effect persists for approximately 45 min. However, the principal conclusion was the extreme difficulty of obtaining truly comparative data at different doses of fentanyl, since this drug alters the setting of the baroreflexes, and both the height and pattern of evoked responses in heart rate are dependent on not only the dose of fentanyl but also the arterial pressure. Without adequate control of the latter, little comment can be made on the comparative quantitative "analgesic" effects of fentanyl when these are measured in terms of change in heart rate.

REFERENCES

Kumagai, Y., Norman, J., and Whitwam, J. G. (1975). *J. Physiol. (Lond.)*, **252**, 36P.

Laubie, M., Schmitt, H., Canellas, J., Roquebert, J., and Demichel, P. (1974). *Eur. J. Pharmacol.*, **28**, 66.

Norman, J., and Whitwam, J. G. (1973). *J. Physiol. (Lond.)*, **234**, 89P.

THE ANIMAL PHARMACOLOGY OF ICI 35 868: A NEW I.V. ANAESTHETIC AGENT

J. B. Glen
Biology Department, ICI Pharmaceuticals Division, Macclesfield, Cheshire

ICI 35 868 (2,6-diisopropylphenol) is a highly lipophilic compound with low water solubility and is solubilized currently with Cremophor EL.

In mice the median hypnotic dose (HD_{50}) of ICI 35 868 is 11.9 mg kg^{-1} and this compares with values of 21.7, 3.3, and 7.9 mg kg^{-1} for thiopentone, Althesin and methohexitone respectively. The therapeutic index obtained with ICI 35 868 is similar to that found with thiopentone. A dose of ICI 35 868 equal to $2 \times HD_{50}$ produced more depression of nocioceptive reflex responses in mice than equivalent doses of thiopentone, methohexitone or Althesin. Depression of respiratory rate in mice following administration of thiopentone and ICI 35 868 was greater than that seen after Althesin or methohexitone. Some excitatory side-effects were seen during recovery from anaesthesia produced by the latter two agents, but not following ICI 35 868 or thiopentone anaesthesia. When given by repeated injection to mice, ICI 35 868 and Althesin showed little evidence of any cumulative effect, whereas the repeated administration of thiopentone produced greatly extended sleeping times.

Anaesthesia has been demonstrated also in the rat, rabbit, cat, pig and rhesus monkey. Anaesthesia was rapid in onset, of short duration, few excitatory side-effects were seen, and good relaxation of skeletal muscle was obtained. Infusions of ICI 35 868 have been given to maintain anaesthesia in rats, cats and pigs for periods up to 5 h. In rats, head lift occurred 6 min after a 1-h infusion of 0.7 mg kg^{-1} min^{-1} and 10 min after a 2-h infusion given at the same rate. In conscious pigs ICI 35 868 2.5 mg kg^{-1} produced an initial hypotensive effect similar to that seen with thiopentone 10 mg kg^{-1} or Althesin 1.8 mg kg^{-1}. The tachycardia produced by thiopentone and Althesin was significantly greater than that produced by ICI 35 868. Cardiac output measured 2 min after injection was increased above pre-injection values with all three agents.

No unexpected interactions were observed when ICI 35 868 was given in conjunction with frequently used inhalation agents, neuromuscular blocking drugs and a range of agents used for pre-anaesthetic medication. In mice chlorpromazine, diazepam and large doses of amylobarbitone increased the sleeping time produced by ICI 35 868, thiopentone and Althesin.

No tissue damage or necrosis was produced by the intentional perivascular or intra-arterial injection of ICI 35 868. These results indicate that ICI 35 868 should produce satisfactory anaesthesia with minimal excitatory effects and with rapid recovery after a single or repeated administration.

ICI 35 868, A NEW I.V. ANAESTHETIC: PRELIMINARY FINDINGS IN 20 PATIENTS

K. M. Rogers, H. K. Adam, K. M. S. Dewar, B. Kay, T. D. McCubbin, A. A. Spence and D. Stephenson
University Department of Anaesthesia, Western Infirmary, Glasgow. ICI Pharmaceuticals, Cheshire. Department of Anaesthetics, University Hospital of South Manchester

ICI 35 868, diisopropylphenol with Cremophor EL 16% w/v in a dose of 2 mg kg^{-1} was used to induce anaesthesia in 20 healthy patients undergoing surgical procedures of intermediate duration; anaesthesia was maintained with a mixture of halothane and nitrous oxide in oxygen. Injected into a vein in the dorsum of the hand over 30 s, ICI 35 868 was found to produce abolition of the eyelash reflex in 57 s (mean ±10.5 SD) from the start of injection. Measurement of heart rate, arterial pressure, respiratory frequency and, in some instances, tidal volume suggest that, while the drug may cause marked but transient respiratory depression, there is little effect on the cardiovascular system.

In most of the patients there was a mildly unpleasant sensation in the hand or arm during injection and in a few there was pain. No other adverse side-effects were observed and the quality of recovery from anaesthesia was satisfactory and unremarkable.

In this double-blind comparison with Althesin in a total of 20 patients, there were fewer instances of excitatory phenomena following ICI 35 868.

GONE BUT NOT FORGOTTEN: BENZODIAZEPINE-INDUCED AMNESIA

P. R. F. Clarke, N. R. Bennett, B. R. Milne and J. A. Thornton
University of Sheffield Medical School

The amnesic effects of diazepam 0.280 mg kg^{-1} or flunitrazepam 0.014 mg kg^{-1} i.v. were studied in 18 volunteers from a medical school population, assigned randomly to two independent treatment groups. Each subject was tested at three stages of a 2-h laboratory session: before injection (pre-test), immediately following injection (peak-test) and 1 h following injection (post-test). Measures of motivation, memory span and general intellectual efficiency were used but will not be reported here.

The amnesic effects were studied using categorized word lists (12 words which the subject was required to categorize first into two named categories and then into four named sub-categories). Each subject was asked to process two such lists in this way, the first in the pre-test period in clear consciousness, the second in the peak-test period when he was having difficulty in staying awake with slurred speech and blurred vision. All but one of the volunteers were slower in "processing" the second list, but all succeeded with only minimal errors. This demonstrated that any subsequent failure of retention could not be attributed to failure of original input of the material. To check the possibility that the amnesic effects might result from difficulty in the recall process itself, the subjects were asked to recall the names in each of the four sub-categories of the first list in the peak-test period just before the second list was presented for processing. Scores ranged from 7 to 12 with a mode of 11 words correct, showing that prompted recall is possible under these conditions.

One hour after injection, the subjects were asked for free recall of the words in both lists and then prompted with the sub-category names. The first list could be recalled efficiently by nearly all subjects (scores ranged from 7 to 12 with a mode of 11 on free recall, and from 9 to 12 with a mode of 12 on prompted recall). The second list (processed at peak-test) was completely inaccessible to free recall for all 18 subjects, and on prompted recall the scores ranged from 0 to 6 with a mode of 0. Thus there would appear to be a severe deficit of retention for material which had been processed successfully at the peak-test. However on a forced-choice recognition test (where the subject is required to rank order three words for probability of being the target word) a new picture emerged. Brown's (1965) measure for this ($\bar{A}$) runs from +1.0 for perfect recognition through 0 for random guessing to −1.0 total misrecognition. For the first list the $\bar{A}$ scores ranged from +0.9 to +1.0, showing near perfect recognition, and for the second list they ranged from −0.08 (the only negative score) up to +1.0, with only four scores worse than +0.25. Thus the material processed had been much better retained than it appeared and significantly affected later behaviour when sensitive measures were used. No substantial differences were found between the drugs.

REFERENCE

Brown, J. (1965). *Br. J. Math. Statist. Psychol.*, **18**, 125.

EVIDENCE FOR HEPATIC METABOLISM OF ALTHESIN RATE-LIMITING THE DURATION OF ANAESTHESIA IN THE RAT

J. W. Sear and J. D. McGivan
University Departments of Anaesthetics and Biochemistry, Medical School Bristol

Previous *in vivo* studies in the rat have shown the effect of phenobarbitone induction, surgical cholestasis and inhibition of microsomal protein synthesis on the sleep-time following a single i.v. dose of Althesin (Novelli, Marsili and Lorenzi, 1975).

We have studied the effect of repeated i.p. injections of Althesin 33 mg kg^{-1} total steroid on the sleep-time in two groups of female Wistar albino rats, weight 200–250 g, and aged 60 days. One group ($n = 16$) was given phenobarbitone 0.1% in drinking water for 7 days before the experiment; a second group ($n = 15$) acted as controls. The phenobarbitone-treated animals showed a decrease in sleep-time to regain the righting reflex (44.3 ± 5.1 min (mean ± SEM); controls 71.2 ± 6.1 min (mean ± SEM) $P < 0.01$). There was no evidence of tolerance developing to repeated administration of Althesin in either group of animals. This is in contrast to the tolerance seen after repeated i.p. injections of ketamine (Livingston and Waterman, 1976).

The cytochrome P450 content of the liver was determined at the end of the experiment in animals from both groups and compared with that present in the livers of normal non-treated rats. Phenobarbitone caused an increase in the cytochrome P450 content, but there was no evidence of self-induction of cytochrome P450 following repeated i.p. injection of Althesin in either the control rats or rats pretreated with phenobarbitone. However, Parikh and Moore (1975) have reported the induction of ALA synthetase (E.C. 2.3.1.37) by repeated i.p. injection of Althesin and some barbiturates in the rat.

There was a significant correlation ($r = -0.869$, $P < 0.01$, $n = 10$) for the hyperbolic relationship between the time to regaining the righting reflex following i.p. Althesin, and the hepatic cytochrome P450 content. The rate of microsomal metabolism of alphaxalone has been studied also *in vitro*, using microsomes prepared from both normal and phenobarbitone fed rats. In the presence of NADPH/NADH and oxygen, metabolism followed normal Michaelis–Menten kinetics. Prefeeding with phenobarbitone led to an increase of V_{max}. There was a significant correlation between V_{max} *in vitro* and the cytochrome P450 content of the microsomes ($r = +0.96$; $P < 0.01$), suggesting that the cytochrome P450 concentration is the rate-limiting step in hepatic metabolism of Althesin.

The results of this study confirm the significant role that hepatic metabolism plays in limiting the duration of anaesthesia following Althesin, especially as the hepatic cytochrome P450 content may be reduced in liver diseases such as cirrhosis and severe hepatitis.

ACKNOWLEDGEMENT

Dr J. Sear is in receipt of an M.R.C. Research Training Fellowship.

REFERENCES

Livingston, A., and Waterman, A. (1976). *Br. J. Pharmacol.*, **57**, 457.

Novelli, G. P., Marsili, M., and Lorenzi, P. (1975). *Br. J. Anaesth.*, **47**, 913.
Parikh, R. K., and Moore, M. R. (1975). *Br. J. Anaesth.*, **47**, 907.

INFLUENCE OF ANAESTHETIC AGENT ON SURVIVAL FOLLOWING ENDOTOXIN SHOCK

P. H. Bavister, *D. E. Longnecker and
C. Prys-Roberts
Department of Anaesthetics, University of Bristol.
**Department of Anesthesiology, University of Virginia, Charlottesville*

Anaesthetics alter the ability of animals to survive shock. In haemorrhagic hypotension halothane prolonged the survival of dogs in comparison with cyclopropane (Theye, Perry and Brzica, 1974) and ketamine increased the survival rate of rats compared with halothane, pentobarbitone or fluoroxene (Longnecker and Sturgill, 1976). In shock induced by superior mesenteric artery occlusion, halothane increased the survival rate of rats when compared with ketamine (Bavister and Longnecker, 1979). We have studied the effects of halothane, Althesin, minaxolone and ketamine on survival rates of rats subjected to endotoxin shock and compared these with an unanaesthetized group of animals.

Dose–response curves were determined for a single batch of endotoxin in male Sprague–Dawley rats allocated randomly to five treatment groups. Doses of endotoxin were calculated on a mg kg^{-1} basis and given i.p., each rat receiving a single dose. Dose intervals were chosen to produce a constant ratio between doses. Four animals were injected at each dose in each of the treatment groups. One hour after injection of endotoxin animals were anaesthetized with halothane 1.2% in air, Althesin 50 mg kg^{-1} i.m., minaxolone 20 mg kg^{-1} i.m. or ketamine 125 mg kg^{-1} i.m. A control group of animals received no anaesthetic. The numbers of survivors 24 h after injection of endotoxin were recorded.

Table I. *LD_{50} values and 95% confidence intervals for endotoxin in the five treatment groups derived by probit analysis. The last line shows the results calculated when the data from all five groups were combined*

	Dose of endotoxin (mg kg^{-1})		
		95% confidence intervals	
Anaesthetic	LD_{50}	Lower	Upper
Awake	7.08	3.04	13.59
Halothane (1.2% inspired)	7.85	4.79	13.85
Althesin (50 mg kg^{-1})	10.52	5.80	48.20
Minaxolone (20 mg kg^{-1})	10.94	5.70	124.70
Ketamine (125 mg kg^{-1})	9.16	3.69	26.24
Combined	9.12	7.00	12.40

Probit analysis of the data failed to show significant differences between the treatment groups. Table I shows the LD_{50} values and 95% confidence intervals. We concluded that with this model we were unable to demonstrate a significant effect of anaesthetic agents on the survival of rats following endotoxin injection.

In order to make the model more sensitive we are repeating the experiment with an unanaesthetized group of rats and a group anaesthetized with Althesin using a fixed endotoxin dose of 9.1 mg kg^{-1}. In addition to survival rates we are measuring arterial blood-gases and biochemical indices of metabolic function.

REFERENCES

Bavister, P. H., and Longnecker, D. E. (1979). *Br. J. Anaesth.*, **51**, 921.
Longnecker, D. E., and Sturgill, B. C. (1976). *Anesthesiology*, **45**, 516.
Theye, R. A., Perry, L. B., and Brzica, S. M. (1974). *Anesthesiology*, **40**, 32.

TRACHEAL INTUBATION CHANGES THE SHAPE OF THE OCCLUSION PRESSURE WAVE

D. H. T. Scott and G. B. Drummond
Department of Anaesthetics, Royal Infirmary, Edinburgh

Minute ventilation is used commonly to measure the influence of depressants such as narcotics and inhalation anaesthetics. Unfortunately, ventilation does not directly estimate central neural activity because factors such as neuromuscular transmission, muscular efficiency, and mechanical changes in the chest wall and lung affect its relationship to "central" activity.

Mechanical properties are less likely to influence the pressure generated by an inspiratory effort against a closed airway, because flow is absent, and volume does not change (apart from the small decompression of thoracic gas). The pressure has been used as an index of central activity and is proportional to diaphragmatic and phrenic activity in experimental animals (Eldridge, 1975).

Derenne and others (1976) studied occlusion pressure in intubated subjects breathing methoxyflurane and found that, although the pressure wave increased in amplitude during carbon dioxide rebreathing, the general shape was not changed. However, our observations of occlusion waves in conscious subjects suggested that the shape of the first part of the wave (before the subject is aware of the occlusion) differed systematically from the shape in intubated subjects and animals with a tracheostomy.

Therefore we have studied anaesthetized patients breathing first from a mask and then after endotracheal intubation. The larynx and trachea were first anaesthetized with topical lignocaine and the subject breathed 70% nitrous oxide and 1% halothane in oxygen from a non-rebreathing system. Inspiration was occluded about every 10 breaths and the pressure generated recorded on a u.v. recorder. Occlusions were repeated after intubation.

The wave shapes were compared by the ratio of the slopes to −0.1 kPa and to 0.1 s. In all six subjects this ratio increased after intubation, because the early part of the curve became steeper (fig. 1).

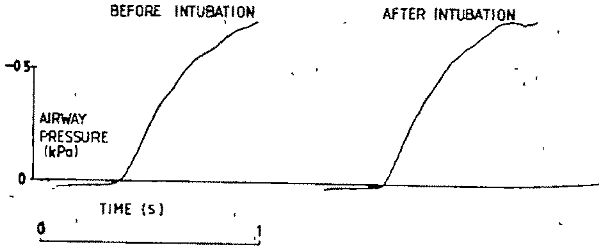


FIG. 1. Airway pressures during occlusion.

We conclude that the first part of the occlusion wave obtained using a mask or mouthpiece may be unsuitable for measurement because upper airway compliance influences pressure transmission from the respiratory muscles.

REFERENCES

Derenne, J.-P., Couture, J., Iscoe, S., Whitelaw, W. A., and Milic-Emili, J. (1976). *J. Appl. Physiol.*, **40**, 805.

Eldridge, F. L. (1975). *J. Appl. Physiol.*, **39**, 567.

ASYNCHRONOUS INDEPENDENT LUNG VENTILATION (AILV)

K. M. HILLMAN AND J. D. BARBER
Department of Anaesthesia, St Bartholomew's Hospital, London

Patients with predominantly unilateral lung pathology sometimes do not respond to conventional respiratory therapy (Glass et al., 1976). Because of a greater compliance most of the delivered minute volume enters the normal lung, possibly exposing it to barotrauma, while the stiff collapsed lung receives a progressively smaller proportion of the total ventilation. Furthermore, when PEEP is used in this situation it may have an adverse effect as, presumably, the compliant alveoli of the unaffected lung preferentially receive the increased pressure causing a decrease in their perfusion and exacerbation of any shunt effect (Kanarek and Shannon, 1975).

Attempts have been made to overcome this problem by ventilating each lung selectively via a double-lumen endobronchial tube (EBT). This can be difficult as the time constants of the alveoli in the pathological lung are different from the alveoli in the normal lung. Independent and flexible control is necessary for the ventilation of each lung. We have approached this problem by using separate ventilators to inflate each lung independently via an EBT, and made no attempt to synchronize them. An optimal ventilation pattern for each lung can be achieved by varying inspiratory rate, tidal volume, respiratory rate and PEEP for each lung.

The four patients on whom we have used SAV had predominantly unilateral pathology which did not respond to conventional measures, including at least 24 h of IPPV and PEEP. We measured cardiac index, pulmonary capillary wedge pressures (PCWP), Pa_{O_2}, Pa_{CO_2} and $\dot{Q}s/\dot{Q}t$ before and during SAV, as well as performing serial chest x-rays. So far, three of our four patients have responded successfully. All respiratory measurements showed considerable improvement, as well as almost complete resolution of the chest x-ray. The patient who did not respond was shown to have extensive fibrosis of his lungs at post-mortem. Furthermore, despite theoretical considerations, cardiac index remained stable in all patients.

During the course of our study a new EBT became available to us. It is constructed of non-toxic material and has high residual volume/low pressure cuffs, making it more suitable for long-term AILV than the currently available red rubber EBTs. We have successfully used this EBT on our last patient.

REFERENCES

Glass, D. D., Tonnesen, A. S., Gabel, J. C., and Arens, J. F. (1976). *Crit. Care Med.*, **4**, 323.

Kanarek, D. J., and Shannon, D. C. (1975). *Am. Rev. Respir. Dis.*, **112**, 457.

ALVEOLAR OXYGEN CONCENTRATION DURING USE OF A CIRCLE SYSTEM WITH CARBON DIOXIDE ABSORPTION

C. M. CONWAY
Westminster Medical School, London

Within a circle system with carbon dioxide absorption one can postulate an "ideal" oxygen concentration, $F\text{s}_{O_2}$, given by the expression:

$$F\text{s}_{O_2} = \frac{\text{Oxygen input in fresh gas} - \text{oxygen uptake}}{\text{Fresh gas flow} - (\text{oxygen} + \text{non-metabolic gas uptake})}$$

or

$$F\text{s}_{O_2} = \frac{\dot{V}\text{F}F\text{F}_{O_2} - \dot{V}_{O_2}}{\dot{V}\text{F} - \dot{V}_{O_2} - \dot{V}\text{AN}}$$

where the suffix F relates to fresh gas and $\dot{V}\text{AN}$ is non-metatolic gas uptake. This assumes an acute steady state, but is independent of gas disposition in the system, inspired gas composition and ventilatory flow. If these latter factors can be defined, forms of the alveolar air equation can be used to determine $F\text{A}_{O_2}$.

In the simplest case, if all fresh gas and expired gas entering the system form a uniform mixture, this mixture will have an oxygen concentration equal to $F\text{s}_{O_2}$ as defined above. The mixture will consist of expired alveolar gas, deadspace gas with an oxygen concentration equal to $F\text{s}_{O_2}$ and fresh gas. Expired gas undergoes a volume decrement equal to $V\text{AE} \cdot F\text{A}_{CO_2}$ as a result of carbon dioxide absorption. Thus

$$F\text{s}_{O_2} = \frac{\dot{V}\text{F}F\text{F}_{O_2} + V\text{AE}F\text{A}_{CO_2}}{\dot{V}\text{F} + \dot{V}\text{AE}\,(1 - F\text{A}_{CO_2})}$$

or

$$F_{A_{O_2}} = F_{S_{O_2}} - F_{A_{CO_2}}\left[F_{S_{O_2}} + \frac{\dot{V}_F(F_{F_{O_2}} - F_{S_{O_2}})}{\dot{V}_{CO_2}}\right]$$

At the opposite extreme, if all fresh gas flows selectively to the lungs and if fresh gas flow does not exceed inspired alveolar minute ventilation, then

$$F_{A_{O_2}} = F_{S_{O_2}}(1 - F_{A_{CO_2}})$$

Other equations can be defined for other forms of gas disposition. These equations are useful in demonstrating the increasing effects that variations in anaesthetic uptake may have on $F_{A_{O_2}}$ as fresh gas flow into the system is reduced.

COMPUTER ASSISTANCE IN THE CONTROL OF DEPTH OF ANAESTHESIA

W. W. Mapleson, R. T. Chilcoat, J. N. Lunn,
M. C. Blewett, M. T. Khatib and B. A. Willis
Department of Anaesthetics,
Welsh National School of Medicine, Cardiff

This study assumed that only the anaesthetist can tell if the depth of anaesthesia existing in a patient is right for that patient at that time, but that he can be aided in achieving the desired depth if, instead of setting the desired inspired concentration by means of the knob on the vaporizer, he sets the desired brain tension by means of a knob on a "black box". The black box must contain a control system which manipulates the vaporizer knob in such a way as to increase the brain tension rapidly to the desired value and then keep it there until some new tension is called for by the anaesthetist.

The present control system, a development of those of Chilcoat (1973) and Mapleson, Allott and Steward (1974), incorporates a mathematical model of the distribution of nitrous oxide and a volatile anaesthetic in the body. The structure of the model is sufficiently elaborate for it to give accurate results provided that it is accurately quantified. Quantification is partly on the basis of normal values, but non-invasive measurements are made in each individual of body mass and, at 10-s intervals, of inspired nitrous oxide and volatile-anaesthetic concentrations and of alveolar ventilation, and, at 10-min intervals, of cardiac output by electrical-impedance cardiography. In addition, occasional samples of arterial blood are taken for the determination of the arterial tension of the volatile anaesthetic. Any difference from the corresponding computed tension is attributed to an error in the impedance estimate of cardiac output and a "true" output is determined by iterative calculation. The system exists as a program, written mainly in Fortran, in an on-line Nova 2 mini computer.

The anaesthetist sets the oxygen and nitrous oxide flowmeters in the usual way and sets the desired brain tension in terms of total MAC units. Every 10 s the system computes the resulting brain tension of nitrous oxide and subtracts this from the desired total MAC units to yield the desired brain tension of the volatile agent; from this the system subtracts the computed brain tension of the volatile agent to yield an "error signal" which, together with other information from the model, quantifies a set of equations for calculating a vaporizer setting which, by the use of arterial "overpressure", rapidly reduces the error with, it is to be hoped, little overshoot or oscillation.

The system has been tested in Alsatian dogs, already made unconscious by i.v. pentobarbitone and subjected to controlled ventilation. Halothane was used as the volatile agent. "Induction" has been achieved in 2 min and control maintained for periods of 50–110 min despite deliberate changes in inspired nitrous oxide concentration, alveolar ventilation, cardiac output (by bleeding) and desired total MAC.

ACKNOWLEDGEMENT

This work was supported by a grant from the Medical Research Council.

REFERENCES

Chilcoat, R. T. (1973). *Br. J. Anaesth.*, **45**, 1235.
Mapleson, W. W., Allott, P. R., and Steward, A. (1974). *Br. J. Anaesth.*, **46**, 805.

IN VITRO LYMPHOCYTE RESPONSES TO MITOGENS IN PATIENTS UNDERGOING A MINIMALLY INVASIVE PROCEDURE UNDER GENERAL ANAESTHESIA

S. Thompson, B. Walton and S. Brailsford
Anaesthetics Unit, The London Hospital, London

Depression of the immune system after general anaesthesia and surgery is now a well-recognized phenomenon and has been implicated in the clinical observations of a high frequency of infections and the spread of metastases after surgery (Walton, 1978). However, the relative importance of the anaesthetic and the surgical components of operative trauma have been difficult to evaluate, particularly in relation to repeated exposures to anaesthesia and surgery.

We have studied 14 women undergoing the minor procedure of insertion of caesium-137 ovoids *per vaginam* for local treatment of carcinoma. General anaesthesia was induced by i.v. Althesin and fentanyl and was maintained for periods of up to 40 min. Blood samples were taken at intervals before and up to 1 week after insertion and the reactivity of the blood lymphocytes was assessed by the *in vitro* lymphocyte transformation test.

The lymphocyte reactivity to the non-specific mitogen phytohaemagglutinin (PHA) and to the specific antigen tuberculin PPD was significantly and maximally depressed within 24 h after induction of anaesthesia, but after 7 days a return to pre-induction values was observed. Reduced *in vitro* lymphocyte reactivity could not be restored by increasing the mitogen concentration.

Six of these patients received a second insertion of caesium-137 ovoids 1 week after the first, thus providing an opportunity to investigate the effects of repeated exposure to anaesthesia on immune depression.

A similar degree of reduced lymphocyte reactivity occurred after the second exposure, but was maximal within 48 h. One week after a second insertion the lymphocyte reactivity had been restored to pre-anaesthetic values.

These changes in lymphocyte reactivity could not be correlated with any changes in absolute lymphocyte numbers.

Patients with malignancy are ill-served by any procedure which may depress their capacity to respond immunologically. Insertion of caesium-137 ovoids under general anaesthesia, although a relatively non-invasive and minor procedure, was followed by a significant depression in *in vitro* lymphocyte reactivity.

There was no indication that a repeated exposure to general anaesthesia and caesium-137 ovoid insertion within 7 days produced any greater degree or duration of this immune depression.

REFERENCE

Walton, B. (1978). *Anaesthesia*, **33**, 322.

ENZYMATIC EVIDENCE OF LIVER DYSFUNCTION FOLLOWING REPEAT ADMINISTRATIONS OF HALOTHANE

G. W. BLACK, J. W. DUNDEE, J. P. H. FEE AND P. D. A. MCILROY
Department of Anaesthetics,
The Queen's University of Belfast, Northern Ireland

Liver function was studied in patients having minor urological or gynaecological operations and requiring two or more repeated anaesthetics each within periods of 30 weeks from the previous one (Fee et al., 1979). All had simple anaesthetic comprising thiopentone-nitrous oxide-halothane. Blood withdrawn before operation and on days 3–5 and 13–15 after operation was analysed for changes in six liver enzymes and the presence of eosinophilia. Data in this report are based on changes in alanine aminotransferase (a.l.t.) and gamma glutamyl transferase (g.g.t.); increases of more than 3 SD of the method of estimation from the initial reading being taken as abnormal.

Of the 143 patients admitted to the study 63 had two administrations of halothane, 22 had three and 10 had four, each within 30 weeks of the previous anaesthetic; none had jaundice or any clinical evidence of liver dysfunction. However, there was a marked increase in frequency of abnormal increases in enzymatic activity with the second and subsequent anaesthetics (table I). The increase in g.g.t. was significant ($P < 0.05$ as determined by the Wilcoxon matched-pairs signed ranks test) at both times of estimation on the second and subsequent administration, but not after the first. These tendencies are paralleled when we consider all six enzymes studied.

The influence of sex, obesity, use of alcohol and tobacco on the occurrence of abnormal enzyme activity after the second administration was analysed. There was a strikingly high frequency ($P < 0.05$) of increase of both a.l.t. (3/14 in obese, 1/40 in non-obese) and g.g.t. (6/14 in obese and 5/40 in non-obese). The other factors showed nothing of significance with these enzymes.

TABLE I. *Percentage frequency of abnormal enzymes on days 3–5 and 13–15 after operation following repeated administrations of halothane*

Halothane administration	G.g.t.		A.l.t.	
	3–5	13–15	3–5	13–15
1st	0	2	8	2
2nd	20	28	7	10
3rd	28	21	18	8
4th	33	28	25	43

These data indicate a high frequency of subclinical liver dysfunction following repeat administration of halothane, particularly in obese patients.

REFERENCE

Fee, J. P. H., Black, G. W., Dundee, J. W., Neill, D. W., Johnston, H. M. L., and McIlroy, P. D. A. (1979). *Br. J. Anaesth.*, **51**, 67P.

EVALUATION OF BREATH-ANALYSERS FOR THE ACCURATE DETERMINATION OF BLOOD ALCOHOL CONCENTRATIONS

W. C. TILSLEY, V. A. BISHOP AND J. P. PAYNE
Research Department of Anaesthetics,
Royal College of Surgeons of England

There has recently been pressure on the British Government to introduce breath-testing apparatus for the determination of blood alcohol concentrations in drivers suspected of exceeding the statutory limit. The present study was carried out in an endeavour to determine the accuracy of breath-analysers for law enforcement purposes.

Experiments were performed on six volunteers, one female and five males aged 20–67 yr and weight 57.3–82.7 kg. On arrival in the department after a light breakfast, each volunteer was shown the equipment and the pattern of the study was explained. A polyethylene catheter was placed in a convenient superficial vein on the left forearm and as soon as the catheter was inserted a control blood sample was withdrawn anaerobically into a 5-ml heparinized syringe. Thereafter the volunteer was encouraged to settle comfortably on a reclining couch and given 150 ml of either whisky or gin suitably diluted over a period of approximately 10 min. Twenty minutes after the completion of drinking the volunteer was asked to breathe in turn through each of seven breath-analysers all of which were available commercially. Each had been calibrated immediately before the experiment started. A blood sample was withdrawn and the procedure was repeated at 20-min intervals for 2–3 h after drinking. The blood was analysed in duplicate on a gas chromatograph.

Graphs were constructed to show the relationship between the blood values measured directly and those derived from breath; and in addition each of the breath-analysers was compared with all others. From these comparisons it became clear that, although each breath-analyser tended to follow the trend of the blood measurements, there was considerable variation in the performance of the different instruments. Compared with direct blood analysis, the breath instruments usually read low but this was not invariable and occasionally readings considerably in excess of the direct determination were obtained.

Of the seven instruments used, two depended on a light change from green through yellow to red and were suitable only for screening purposes. Two instruments had analog outputs, but were not sufficiently consistent for quantitative assessment. The remaining three machines had digital outputs and two of these, the most accurate of the seven studied, were fairly sophisticated in the method of handling the sample, but rather large compared with the other instruments, which could be held comfortably in one hand. Nevertheless, none proved sufficiently accurate to justify its use for the determination of blood alcohol concentrations for law enforcement purposes, but with the exception of the light indicators they could be used with advantage for screening.

EFFECT OF HALOTHANE ON THE PERFORMANCE OF MYOCARDIUM SUPPLIED BY A NARROWED ARTERY

C. M. Francis, E. Lowenstein, W. L. Davies,
P. Foëx and W. A. Ryder
Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford

The effect of halothane on the performance of the myocardium has been studied in normal hearts and hearts where one or more of the major coronary arteries have been occluded. There are, however, no data on its effect on myocardium supplied by a narrowed artery. The use of a narrowed coronary artery is more likely to mimic the conditions of patients with coronary artery disease than those models that employ complete occlusion of a coronary artery.

In 13 dogs, the effects of stepwise increases of halothane concentration (0.5% to 2%) on global and regional function have been studied before and after critical constriction of the left anterior descending coronary artery (LAD). Regional function was evaluated using miniature ultrasonic length transducers implanted in the sub-endocardial muscle supplied by either the LAD or the left circumflex coronary artery (LC). The LAD was constricted below its first diagonal branch by a micrometer controlled snare. E.c.g., aortic, left ventricular and left atrial pressures, LV$dP/dt$ and the length signals were recorded. Critical constriction of the LAD was obtained by tightening the snare (under 0.5% halothane anaesthesia), until performance of this segment was impaired; the snare was then released by small amounts until performance returned to normal. The constriction was judged to be critical if 90 s of hypoxia caused dysfunction in the narrowed segment but not in the control segment.

Dose-dependent reductions of mean arterial pressure (up to 36%) and of LV$dP/dt$ max (up to 48%) and increases of LVEDP (up to 1.2 kPa) were observed in response to the increasing concentrations of halothane before critical constriction of the LAD. Dose-related reductions in shortening were observed in both segments. After critical constriction the dose-dependent effects of halothane on global function were similar to those observed before constriction. However, the LAD segment showed a much greater depression of shortening (table I) whilst the LC behaved as before. In eight of 13 animals paradoxical systolic lengthening and post-systolic shortening were observed.

Table I. *Percent decrease of systolic shortening in response to different concentrations of halothane (mean ± SEM of 13 experiments)*

	Halothane (%)		
	1%	1.5%	2%
LAD segment			
Pre-constriction	7.8 ± 2.8	21.5 ± 4.7	34.1 ± 5.8
Post-constriction	12.5 ± 3.1	30.0 ± 6.6	67.2 ± 10.4
P	< 0.05	< 0.001	< 0.001

These experiments indicate that halothane causes more depression of myocardium supplied by a narrowed coronary artery than of myocardium supplied by a normal coronary artery. Depression of the narrowed segment may be so severe that contraction becomes paradoxical. Profound impairment of regional function because of narrowing of the LAD is not accompanied by changes in those haemodynamic variables that are commonly measured in clinical practice.

EFFECT OF FOOD AND MILD EXERCISE ON INDIVIDUALS SUSCEPTIBLE TO MALIGNANT HYPERPYREXIA

I. T. Campbell,* F. R. Ellis and R. Evans
Leeds University (St James's) Hospital, Leeds
(**Present address: Royal Liverpool Hospital, Liverpool*)

It has been claimed that pigs susceptible to malignant hyperpyrexia (MHS) have basal metabolic rates greater than normal animals (Williams et al., 1978). MHS pigs are prone to develop an acute hyperpyrexic episode during exercise and with stress. Although the same has been claimed for man, the only supporting evidence is anecdotal. No systematic studies appear to have been made of heat production in human MHS individuals either at rest, or exercising, or under any form of stress.

Heat production (metabolic rate) was measured by indirect calorimetry in nine MHS individuals and nine control subjects at rest and whilst performing a standard work load of 67 W on a bicycle ergometer. Measurements were made both fasting and following a 2510-kJ (600-kcal) meal of 135 g of "Complan" in water. Blood samples were taken at the end of each measurement period and analysed for glucose, insulin, triglycerides, creatine phosphokinase, thyroxine, cortisol, lactate and pyruvate.

There was no difference in heat production between the MHS and control groups at rest, either fasting or fed, or exercising fasting. Mean resting metabolic rate of both groups measured from the 30th to the 55th min after the meal increased by 12% ($P<0.001$) demonstrating the normal phenomenon of dietary induced thermogenesis. Heat production of the control group exercising for 20 min 1 h after the meal was 1.46 kJ (0.35 kcal) min^{-1} (7%) greater than the fasting measurement ($P<0.001$), but in the MHS group heat production exercising after the meal was the same as it had been before, that is dietary thermogenesis during exercise was absent.

The glucose/insulin ratios of the MHS group were smaller than those of the controls and there were other differences in hormone concentrations both at rest and in response to food and exercise. In the controls exercise was associated with a statistically significant increase ($P<0.05$) in plasma thyroxine, the value subsequently declining at rest. Exercise in the MHS group produced no such change in plasma thyroxine. Plasma cortisol concentration was generally greater in the control group than in the MHS group, a difference which was significant with the combination of food and exercise.

Differences were evident in the concentrations of metabolites measured. The triglyceride concentration in the controls remained constant throughout the experiment but tended to increase in the MHS group. In the control subjects the plasma lactate showed the expected increase with exercise and decreased with rest. This was not seen in the MHS subjects, where the only change was a gradual but persistent increase throughout the experiment. Pyruvate concentration in the controls increased with exercise and with ingested food but, in the MHS group, decreased following the standard meal.

It is concluded that metabolic rates of MHS subjects at rest or during mild exercise are the same as those of normal subjects. There is evidence, however, that there are differences in the metabolic and endocrine response to food and mild exercise of these subjects compared with normal individuals.

REFERENCE

Williams, C. H. et al. (1978). In *Second International Symposium on Malignant Hyperthermia* (eds J. A. Aldrete and B. A. Britt). New York: Grune and Stratton Inc.

EFFECT OF TOBRAMYCIN ON MAMMALIAN NERVE-MUSCLE PREPARATION

J. P. Corrigan, A. Wilson and D. P. O'Mahony
Departments of Pharmacology and Physiology,
University College, Cork, Eire

Waterman and Smith (1977) reported interference with neuromuscular transmission in a patient who received tobramycin after operation. We decided, therefore, to test the effect of tobramycin on the rat phrenic nerve–diaphragm preparation.

The preparation was suspended in Krebs solution (double glucose) at 35 °C, and bubbled with 95% oxygen–5% carbon dioxide. Isotonic substitution of $NaHCO_3$ for NaCl was used to increase the bath pH to 7.6, when required. Indirect supramaximal stimulation (4 V, 0.2 ms, 0.1 Hz) was provided by a Grass S.44 stimulator. Twitches were recorded isometrically by an "Ether" strain gauge, 56 g maximum response, driving a "Devices" polygraph. The bath pH was monitored in all experiments. Before addition, the pH of tobramycin was titrated to bath pH with HCl, to prevent an increase in pH of the bath from producing a dose-dependent facilitation.

A dose-dependent decrease in contractions occurred when tobramycin was added in a concentration range from 2.5 to 7 mmol litre^{-1}, at pH of 7.4, and from 6 to 13 mm litre^{-1} at pH of 7.6. De Rosayro and Healy (1978) reported only a dose-dependent facilitation, in a lower dose range.

Incomplete reversal was achieved with neostigmine 2.5 μg ml^{-1} and $CaCl_2$ 5 mmol litre^{-1}. The most effective reversal was achieved by bubbling the bath with 100% oxygen, which increased the pH to 8.1 (fig. 1).

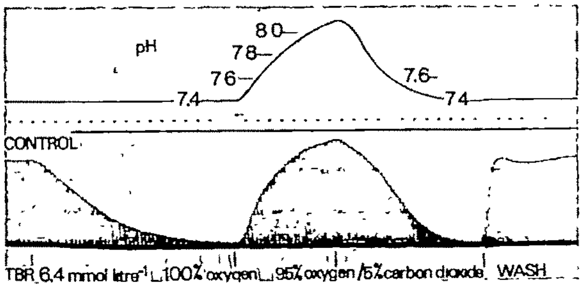


FIG. 1. Upper trace shows pH changes which occurred during the course of the experiment. Lower trace muscle twitch. Block achieved after addition of tobramycin 6.4 mmol litre^{-1} and reversal by bubbling with 100% oxygen with consequent increase in pH.

Aminoglycoside block is considered to resemble magnesium block, in many respects. However, magnesium block does not show pH dependence. The tobramycin block appears to be related to its ionization and with pKa 7.5, the ionization is very sensitive to changes in pH in this range. At pH 8.1, the ionization is less than that at pH of 7.4 and tobramycin is then a less potent neuromuscular blocking agent. Stanley, Giesecke and Jenkins (1969) reported antagonism of neomycin block in cats by $NaHCO_3$. We have found that neomycin block is also reversed by bubbling with oxygen (unpublished).

The findings suggest that reversal of acidosis might be of value in antagonizing any interference with neuromuscular transmission, in which either tobramycin or neomycin is implicated.

ACKNOWLEDGEMENT

We wish to acknowledge the generous gift of tobramycin from Eli Lilly & Co.

REFERENCES

de Rosayro, M., and Healy, T. E. J. (1978). *Br. J. Anaesth.*, **50**, 251.

Stanley, V. F., Giesecke, A. M., jr and Jenkins, M. T. (1969). *Anesthesiology*, **31**, 228.
Waterman, P. M., and Smith, R. B. (1977). *Anesth. Analg. (Cleve.)*, **56**, 587.

EXPERIMENTAL STUDIES WITH ATRACURIUM, A NEW NEUROMUSCULAR BLOCKING AGENT

R. HUGHES AND D. J. CHAPPLE
Pharmacology Laboratory,
The Wellcome Research Laboratories, Beckenham, Kent

Atracurium is one of a series of neuromuscular blocking agents which has been developed in an endeavour to overcome some of the disadvantages of such drugs currently in general use (Stenlake, 1978). Studies in laboratory animals have been carried out using techniques described previously (Hughes and Chapple, 1976a, b) to assess the clinical potential of this agent.

Atracurium 0.5–1.0 μg ml^{-1}, like other non-depolarizing drugs, caused neuromuscular blockade of the chick biventer-cervicis preparation without producing the initial contracture characteristic of the depolarizing agents.

In six cats anaesthetized with chloralose, i.v. doses of 0.25 or 0.5 mg kg^{-1} were sufficient to produce complete neuromuscular paralysis of the tetanic and single twitch responses of the gastrocnemius muscles within 1–2 min. Full recovery of both responses occurred within 37 ± 2.0 (mean ± SEM) min, neuromuscular paralysis was antagonized by neostigmine 0.05 mg kg^{-1} i.v. Dose–response curves showed that vagal blockade only became of importance after doses of 2 mg kg^{-1} i.v., that is at eight times the full neuromuscular paralysing dose; heart rate was unchanged. Sympathetic blockade was evident after supramaximal doses of 4 mg kg^{-1} (that is $18.2 \pm 10.9\%$ inhibition) when systemic arterial pressure was reduced by a mean of $34 \pm 5.4\%$. Similar results were obtained in seven rhesus monkeys anaesthetized with thiopentone and nitrous oxide.

Evidence of histamine release was obtained only after large doses of atracurium were administered to two dogs anaesthetized with chloralose. I.v. doses of mepyramine 10 mg kg^{-1} and burimamide 15 mg kg^{-1} were sufficient to abolish the hypotension induced by histamine 20–40 mg kg^{-1} i.v. These doses of the H_1 and H_2-receptor antagonists reduced the hypotension caused by atracurium 2 mg kg^{-1} (that is eight times full paralysing dose) from 52 to 16% and 42 to 25% respectively in each dog.

In controlled experiments in six anaesthetized cats, there was no significant difference in the neuromuscular paralysing potency and the time taken for full recovery when atracurium was administered directly into the circulation *via* the jugular vein, or through the liver *via* the hepatic portal vein or after the renal artery, vein and ureter of each kidney had been ligated. Thus, it is unlikely that either the liver or the kidneys play a major role in the elimination of the drug.

Incubation of atracurium with human plasma at 37 °C showed that it undergoes an enzymatic ester hydrolysis with a half-life of 22 min. Similar experiments in appropriate buffers have shown that the drug also undergoes a non-enzymatic decomposition which was three times faster at pH 7.6 than at pH 7.1. Furthermore, in eight anaesthetized cats the neuromuscular paralysing potency of atracurium was reduced significantly ($P < 0.01$) after the pH of the arterial blood was increased from 7.31 ± 0.01 to 7.63 ± 0.02 by hyperventilation.

REFERENCES

Hughes, R., and Chapple, D. J. (1976a). *Br. J. Anaesth.*, **48**, 59.
—— —— (1976b). *Br. J. Anaesth.*, **48**, 847.
Stenlake, J. B. (1978). *Adv. Pharmacol. Ther.*, **3**, 303.

PRELIMINARY STUDIES WITH ATRACURIUM IN ANAESTHETIZED MAN

T. M. HUNT, R. HUGHES AND J. P. PAYNE
Research Department of Anaesthetics,
Royal College of Surgeons of England and
St Peter's Hospitals, London

Atracurium is a potent non-depolarizing neuromuscular blocking agent with a wide separation between the neuromuscular paralysing dose and that causing cardiovascular side-effects in laboratory animals (Hughes and Chapple, 1980). On the basis of satisfactory experimental studies a preliminary evaluation of this drug has been carried out in 28 anaesthetized patients using techniques previously described (Hughes, Ingram and Payne, 1976).

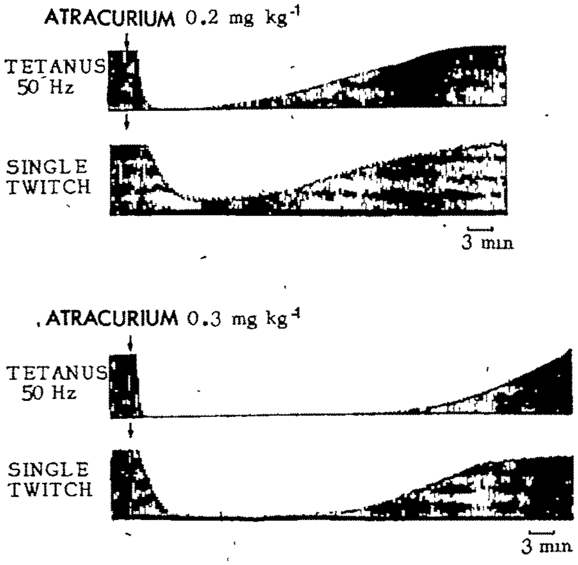


FIG. 1. Effects of atracurium on the tetanic and single twitch responses of the adductor pollicis muscle.

In a group of 10 patients, an i.v. dose of atracurium 0.2 mg kg^{-1} was sufficient to cause complete paralysis of the tetanic responses of the adductor pollicis muscle, but a dose of 0.3 mg kg^{-1} was required to block the single twitch responses (fig. 1). Blockade was of medium duration and was readily antagonized by neostigmine 2 × 2.5 mg. The e.c.g., heart rate, systemic arterial pressure and central venous pressure were unchanged. In two patients endotracheal intubation was accomplished in 1.5 and 2 min respectively after administration of atracurium 0.25 and 0.3 mg kg^{-1} when the vocal cords were relaxed.

A further eight patients were given a dose of 0.6 mg kg^{-1} when hypotension ($4 \pm 1.8\%$) (mean $\pm$SEM) and increases in heart rate ($4 \pm 1.0\%$) were minimal. In two patients tracheal intubation was performed within 1 min of receiving the drug and full block was completely reversed after 10 and 20 min respectively by neostigmine 2×2.5 mg.

Three patients, who were given 1% halothane throughout, received atracurium 0.2 mg kg^{-1} and another patient received 0.6 mg kg^{-1}. Systemic arterial pressure and heart rate were unchanged and recovery from neuromuscular blockade was not prolonged.

Finally, six patients received an initial dose of 0.3 mg kg^{-1} and three of these patients were subsequently given three to six incremental doses of 0.05 mg kg^{-1} at regular intervals and three patients were given two to four doses of 0.1 mg kg^{-1}. In each patient the magnitude of the block and the rate of recovery were dose-related and this consistent pattern may be taken as evidence of the lack of cumulative effects.

REFERENCES

Hughes, R., and Chapple, D. J. (1980). *Br. J. Anaesth.* (in press).

—— Ingram, G. S., and Payne, J. P. (1976). *Br. J. Anaesth.*, **48**, 969.

THE ROLE OF CIRCULATING MICROAGGREGATES IN THE DEVELOPMENT OF HYPOXAEMIA AFTER OPERATION

I. T. CAMPBELL AND C. N. MCCOLLUM
University Departments of Anaesthesia and Surgery, Leeds University, St James's Hospital, Leeds

Hypoxaemia after operation is a well-recognized complication of surgery and anaesthesia. It has been ascribed to depressant effects of analgesics and anaesthetics, atelectasis, and the effect of anaesthesia and pain on lung volumes. In trauma patients, attention has focused recently on the possible role of intravascular platelet aggregates (IPA) in pulmonary damage following shock. The present investigation was undertaken to investigate the role of microaggregates in hypoxaemia after operation.

A modification of the screen filtration pressure (SFP) technique of Swank (1961) has been devised, enabling the development of micro aggregates to be identified *in vivo* (McCollum, 1978).

Twenty patients undergoing elective major abdominal surgery gave written informed consent. Arterial Po_2 and ($PA_{O_2} - Pa_{O_2}$) were measured before operation. SFP was measured in femoral vein blood obtained 0.5 h and 3 h after operation. Depending on the result of these measurements, patients were allocated to one of two groups—those who developed micro aggregates (IPA +ve) and those who did not (IPA −ve). Arterial Po_2 and ($PA_{O_2} - Pa_{O_2}$) were measured again 7 days after surgery.

On the first day after operation there was no difference between the two groups with respect to Pa_{O_2} or ($PA_{O_2} - Pa_{O_2}$). One week after surgery the mean Pa_{O_2} of the IPA +ve group was 1.8 kPa smaller than the value before operation and the Pa_{O_2} of the IPA −ve group 0.6 kPa less than the value before operation. The difference between the two groups was significant ($P < 0.05$) (Mann–Whitney *U* test). ($PA_{O_2} - Pa_{O_2}$) of the IPA +ve group increased by 2.3 kPa, and that of the negative group by 0.4 kPa ($P < 0.01$).

Mean platelet count of the IPA +ve group decreased by 81.7×10^9 1 day after surgery and by 21.4×10^9 in the IPA −ve patients. This difference was significant ($P < 0.025$). There was no difference between the two groups with respect to age, medication, smoking habits or pre-existing pulmonary disease. Six of the IPA +ve group and three of the IPA −ve group received blood. There was no significant difference in the changes in Pa_{O_2} or ($PA_{O_2} - Pa_{O_2}$) between patients who received blood and those who did not.

We conclude that intravascular platelet aggregates can be demonstrated in patients undergoing elective major surgery and the formation of these aggregates is associated with hypoxaemia 1 week after surgery.

REFERENCES

McCollum, C. N. (1978). *Br. J. Surg.*, **65**, 813.

Swank, R. L. (1961). *N. Engl. J. Med.*, **265**, 728.

Br. J. Anaesth. (1980), **52**, 241

CORRESPONDENCE

CONSCIOUSNESS DURING ANAESTHESIA

Sir,—The introduction and acceptance of the term "awareness" into the vocabulary of anaesthetists has been unfortunate. It has brought with it a tendency to regard consciousness during general anaesthesia as being acceptable in a small percentage of cases and to view its occurrence as a minor complication. The description contained in your Editorial (1979) records the appalling realities and is similar to the experience of a personal friend who was awake through most of an emergency hysterectomy carried out for post-partum haemorrhage.

I suggest that anaesthetists should abandon the term and their faith in the potency of poorly supplemented nitrous oxide; unconsciousness is an essential component of general anaesthesia and measures must be taken to ensure that the fear, held by many patients, of waking up in the middle of the operation is never realized.

L. V. H. MARTIN
Edinburgh

REFERENCES

Editorial (1979). On being aware. *Br. J. Anaesth.*, **51**, 711.

EXTRADURAL SPACE

Sir,—I was interested to read the article by Dr Sharrock (1979) concerning false-positive loss of resistance when locating the lumbar extradural space. Dr Sharrock comments that it can be impossible to distinguish between false and true entry into the space.

A simple test I use to differentiate between the two is as follows. As soon as the needle is thought to have entered the extradural space, inject 2–3 ml of air rapidly. Normally the patient feels nothing or sometimes a sensation of pressure. However, if he or she flinches or complains of pain or both, then the needle is unlikely to be in the extradural space. This test is also valuable when the ligaments are unusually soft and there is no loss of resistance at all.

M. DUCROW
Solihull, Warwickshire

REFERENCE

Sharrock, N. E. (1979). Recordings of, and an anatomical explanation for, false positive loss of resistance during lumbar extradural analgesia. *Br. J. Anaesth.*, **51**, 253.

PHARMACOKINETICS OF MINAXOLONE

Sir,—Minaxolone, the latest and water-soluble steroid anaesthetic agent, would appear to have many characteristics desired of an i.v. induction (and possibly maintenance) agent. Its onset of action has been reported as rapid (Aveling et al., 1979; Davis et al., 1979), it is painless to inject (Dundee, 1979) and recovery time is short (Dundee, 1979). In addition, and in contrast to barbiturates, repeated doses in mice were reported to produce little cumulative effects (Davis et al., 1978). The latter property would be assumed to relate to the comparative pharmacokinetics of the agent. Dundee (1979) commented that the pharmacokinetics of minaxolone were not known. We have recently completed a preliminary study of the pharmacokinetics of minaxolone given as subanaesthetic infusions in five healthy volunteers. In these subjects, the mean total body clearance (blood) of minaxolone was 1.6 litre min^{-1},—an average value comparable to total liver blood flow in normal man. Renal clearance was negligible ($<1\%$ total clearance), confirming our studies in sheep (in preparation) which revealed total liver extraction. Other mean pharmacokinetic properties (Hull, 1979) included: central compartment volume 58 litre, steady state volume of distribution 159 litre, fast half-life 8 min and slow half-life 80 min. Our studies conclude that rapid recovery after minaxolone and lack of cumulative effects with repeated doses may be explained by the extremely high clearance and appreciable body redistribution.

L. E. MATHER
L. T. SEOW
G. K. GOURLAY
J. G. ROBERTS
M. J. COUSINS
Australia

REFERENCES

Aveling, W., Chang, H., Clements, E., Waters, A., Savege, T. M., Campbell, D., Fitch, W., Prys-Roberts, C., Sear, J. W., and Simpson, P. (1979). Early clinical evaluation of minaxolone, a new steroid i.v. anaesthetic agent. *Br. J. Anaesth.*, **51**, 564P.

Davis, B., Dodds, M. G., Dolamore, P. G., Gardner, C. J., Sawyer, P. R., Twissell, D. J., and Vallance, D. K. (1979). Minaxolone: a new water soluble steroid anaesthetic. *Br. J. Anaesth.*, **51**, 564P.

Dundee, J. W. (1979). New i.v. anaesthetics. *Br. J. Anaesth.*, **51**, 641.

Hull, C. J. (1979). Pharmacokinetics and pharmacodynamics. *Br. J. Anaesth.*, **51**, 579.

INEFFICIENCY OF ANTACID IN PREVENTION OF ASPIRATION PNEUMONIA

Sir,—We read with great interest "Aspiration syndromes in pregnancy" (Heaney and Jones, 1979). We would like to suggest a possible mechanism for the apparent failure of antacid preparations to prevent acid pulmonary injury following aspiration. The typical antacid solutions used today are thick suspensions and *in vitro* experiments in our laboratory have shown that they are inefficient agents for neutralizing gastric juice (fig. 1). Following the mixing of such antacid solutions with gastric juice, a two-layer solution often results. The pH of the top layer of the solution (gastric juice) is less than that of the bottom layer (antacid). When a nasogastric tube is inserted immediately after the induction of general anaesthesia in patients who have received antacid, gastric juice is often aspirated first, followed by the thick antacid solution. This indicates that similar conditions exist in the stomach *in vivo* as in the

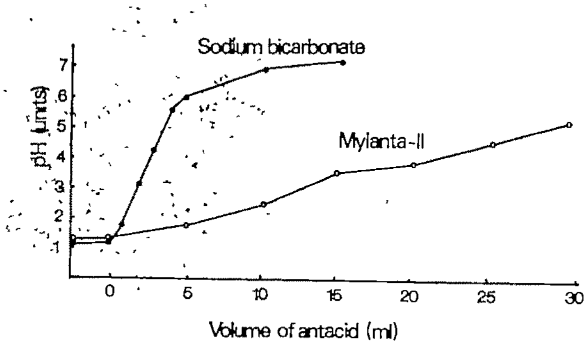


FIG. 1. Amount of sodium bicarbonate 1 mol litre^{-1} and Mylanta–II solution required to neutralize 30 ml of gastric juice with pH 1.1 from a patient with cerebral aneurysm.

in vitro test. This could explain acid pulmonary injury in patients who aspirate even after the administration of antacid. Our most recent study (Toung and Cameron, 1979) demonstrates that routine administration of cimetidine before operation can reduce gastric acidity very effectively and may be helpful in avoiding aspiration pneumonia following anaesthesia. However, we still feel the most appropriate action is to exercise all precautionary measures at the time of induction, in addition to the administration of an appropriate prophylactic agent.

T. TOUNG
J. L. CAMERON
Baltimore, U.S.A.

REFERENCES

Heaney, G. A. H., and Jones, H. D. (1979). Aspiration syndromes in pregnancy. *Br. J. Anaesth.*, **51**, 266.

Toung, T., and Cameron, J. L. (1979). Cimetidine as a routine preoperative medication. *Surgery* (in press).

I.V. EQUIPMENT DESIGN AND INFECTION

Sir,—Dr Peters and his colleagues (1979) have raised an important point about i.v. catheters. In this context of equipment design, is it perhaps not time to take a serious look at the most common and dangerous complication of long-term i.v. equipment, namely infection? Whilst careful techniques and perhaps the use of heparin (Bailey, 1979) can greatly reduce the frequency of this problem, it is not avoidable entirely. Taps may constitute an open invitation to bacterial entry to the circulation and are a particular hazard (Dryden and Brickler, 1979; Walrath et al., 1979). Should we avoid their use whenever possible, and use the much older technique of direct injection into a rubber connection since, unlike a tap, this is a surface which can be sterilized easily and quickly? Perhaps manufacturers should be asked to turn their attention to the design of a new type of device for the intermittent and completely sterile i.v. administration of drugs.

ALAN GILSTON
London

REFERENCES

Bailey, M. J. (1979). Reduction of catheter-associated sepsis in parenteral nutrition using low dose intravenous heparin. *Br. Med. J.*, **1**, 1671.

Dryden, G. E., and Brickler, J. (1979). Stopcock contamination. *Anesth. Analg.* (*Cleve.*), **38**, 141.

Peters, J. L., Mehtar, S., Vallis, C. J., and Kenning, B. R. (1979). Central venous catheter design and maintenance complications. *Br. J. Anaesth.*, **51**, 805.

Walrath, J. M., Abbott, N. K., Caplan, E., and Scanlan, E. (1979). Stopcock bacterial contamination in invasive monitoring systems. *Heart Lung*, **8**, 100.

DELAYED BLOCKAGE IN AN EXTRADURAL CATHETER

Sir,—A 24-yr-old primigravid woman was given extradural analgesia for moderate systemic hypertension (diastolic pressure 90–100 mm Hg) and slight proteinuria. The Lee catheter was inserted through a disposable Tuohy needle at the L3–4 interspace and 3 cm placed in the extradural space. A test dose of 1.5% plain lignocaine 2 ml was followed by a dose of 10 ml. A satisfactory decrease in arterial pressure and good pain relief resulted. Forty minutes later, 0.375% plain bupivacaine 10 ml was administered. About 75 min later it was impossible to inject any solution through the catheter despite withdrawing it incrementally by 2 cm. On removal it was revealed that the side holes of the Lee catheter were sealed by blood clot (fig. 1). A new catheter was placed at L2–3, satisfactory extradural analgesia achieved and labour progressed uneventfully thereafter.

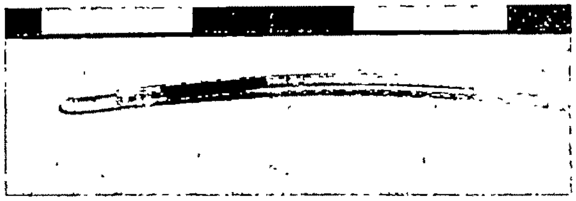


FIG. 1. Extradural catheter with cm scale.

As the first catheter had allowed the free passage of 2 ml, 10 ml and 10 ml boluses of drug in a period of 1 h, it is possible that the haemorrhage which caused blockage occurred after this time. The movement of the patient in bed may have caused the tip of the catheter (which is smooth, rounded and with no end-hole) to rupture a vessel in the extradural plexus of veins.

Recent correspondence (Galloon, 1978; Scott, 1978; Rees and Rosen, 1979) has highlighted the possibility of catheter migration into the subdural space with consequent induction of a late spinal block. This case suggests that there may also be a risk of delayed i.v. injection. Awareness of both possibilities is necessary in the practice of extradural catheter techniques.

D. G. RAITT
Leicester

REFERENCES

Galloon, S. (1978). Test doses in extradural analgesia. *Br. J. Anaesth.*, **50**, 304.

Rees, G. A. D., and Rosen, M. (1979). Test-dose in extradural analgesia. *Br. J. Anaesth.*, **51**, 70.

Scott, D. B. (1978). Test doses in extradural analgesia. *Br. J. Anaesth.*, **50**, 304.

Br. J. Anaesth. (1980), **52**, 243

BOOK REVIEWS

Outpatient Anaesthesia. Edited by Burnell R. Brown, jr. Contemporary Anaesthetic Practice Series. Published by F. A. Davis Co., Philadelphia. Pp. 96. Price $10.00.

This book, first in a new series, deals with the problems of anaesthesia for ambulatory surgical patients as experienced by the Ambulatory Surgical Center at Tucson Medical Center, U.S.A. The publication of such a book comes at a time when it should prove to be attractive, particularly to the United Kingdom reader, where the alarming increase in inpatient waiting lists is forcing surgeons to consider ways in which the crisis can be tackled.

The preface promises the reader "a thorough discussion of the facilities, personnel, economics, patient selection and care, techniques and drug selection". It is with regret that the reviewer must admit to some disappointment, as this promise is not fulfilled in the subsequent 96 pages. Perhaps this is in part a result of the fact that the text reflects North American practice in both anaesthesia and surgery. The section on Drug Interactions is particularly disappointing as it is by no means comprehensive and omits several common and potentially dangerous problems associated with preoperative drug therapy.

It will come as no surprise that the text contains a chapter on monitoring. Happily, the preface to this chapter warns the reader that the sophisticated equipment subsequently mentioned must not replace the vigilance of the trained anaesthetist. One wonders what place, if any, have some of the devices in outpatient anaesthesia.

The section on regional anaesthesia is superficial and does not reflect the important note this form of anaesthesia has to play in outpatient surgery.

The expertise of the anaesthetist in the management of the surgical outpatient embraces the problem of chronic pain and the reader will be interested in statistics related to the types of condition encountered.

In view of what has been stated in this review the reader may not be roused to read this small book. However, two valuable chapters on "The Ambulatory Surgery Center" and "The Surgicenter" give a clear insight into the logistics of what is a successful facet of surgical practice in North America.

The anaesthestist contemplating involvement in "Day-care surgery" is well advised to read this book as he may find some useful hints on the setting-up and development of this service. Apart from these two chapters, he will find little which he does not already know.

J. A. Thornton

Dangerous Mistakes in Drug Administration: 1979. Medico-Pharmaceutical Forum. Obtainable from The Medico-Pharmaceutical Forum, 1, Wimpole Street, London W1M 8AE. Price 50p.

Anaesthetists prescribe and administer drugs. Most anaesthetics involve the use of several drugs and in some situations such as cardiac surgery it may be wise to have readily available a number of drugs which may not be used. Anaesthetists are thus particularly at risk of prescribing or administering a dangerous dose of a drug. The Medico-Pharmaceutical Forum has published a report describing a number of accidents where the wrong drug or the wrong dose was given. Mistakes have occurred with orders given verbally ("Inderal"—propanolol being given to a patient with asthma instead of "Intal"—disodium chromoglycate); with the failure to read the ampoule (adrenaline instead of atropine); with the change of suppliers (a change from "Scoline" to "Anectine" led to suxamethonium being given instead of atropine); and with the replacement of the wrong drug into a pack. I have seen digoxin ampoules being placed in tubocurarine packs—the ampoules were identical except for the names of the drugs.

The report suggests how to avoid some of these mistakes. Nursing staff use a double check for all injections: anaesthetists must make a conscious effort to read every ampoule. Perhaps they should also draw up the contents themselves. These are the essential safeguards, but other measures can help. Transfers of ampoules from manufacturers' packs to other containers should be minimized and once an ampoule is removed it should never be replaced. The report also suggests that manufacturers should help with clearer labelling, emphasizing the approved name and giving the amount of drug present rather than the concentration, but the responsibility lies with those who prescribe and administer the drug. The report does not make elegant reading, but it should be studied in all anaesthetic departments and hospital pharmacies.

John Norman

Clinical Pharmacology: Basic Principles in Therapeutics, 2nd edn. Edited by K. L. Melmon and H. F. Morrelli. Published by Macmillan Publishing Co., Inc., New York. Pp. 1146; illustrated; indexed. Price £18.

This large American book does not claim to be a textbook of pharmacology. Rather, it hopes to supplement such texts by helping ". . . stimulate scholarly and rational thought about therapeutics . . .". That it certainly does.

The early chapters constitute a superb introduction to clinical pharmacokinetics which could hardly be bettered. These basic principles are then rigorously applied to a wide range of clinical problems by a galaxy of eminent physicians, pharmacologists and pharmacists.

If you believe that "clinical pharmacology is that bit of pharmacology which interests physicians", then the topics are well covered. If one feels that the subject could have a somewhat wider definition, then the book is a disappointment, since many familiar drugs are not mentioned, and others given scant attention. For instance, opiates are tucked away in a chapter on "Neurologic Disorders", and briefly discussed by a professor of psychiatry and medicine whose knowledge is apparently limited to morphine, pethidine and pentazocine. Some anaesthetic drugs *do* appear here and there. Halothane, we are assured on p. 395, "should never be used for minor procedures such as tonsillectomy or breast biopsy, so as to avoid the risk of an adverse reaction when it is used as the main agent for a major operation such as a porto-caval shunt", so I suppose we should not complain too much. We are also told (in the otherwise excellent section on respiratory failure) that "an unconscious patient's head should be tilted backward as far as possible to open the nasopharynx and permit breathing."

It is, of course, easy to find numerous errors and omissions in a book of this size, and to wonder at the inclusion of such philosophical chapters as "Qualitative Aspects of Therapeutic Decision Making" and "Economics and Epidemiology of Drug Use", but this should not detract from its overall quality. Many chapters, especially those on cardiovascular and respiratory systems, give an account of scientific therapeutics which is in a class of its own. The section on drug reactions and interactions is well classified and truly comprehensive.

As a work of reference, this book should find a place in every departmental library, and the "basic principles" chapters are especially commended to those preparing for the primary F.F.A.R.C.S.

C. J. Hull

Monitoring Patients in The Operating Room. Edited by J. S. Gravenstein, R. S. Newbower, A. K. Ream and N. Ty Smith. Published by Charles C. Thomas, Springfield, Illinois. Pp. 270; illustrated; indexed. Price $22.50.

In April 1977, sponsored by a consortium of instrumentation companies, a workshop on "Patient Monitoring in the Operating Room" was held in Cleveland, Ohio, with 17 contributors and 35 guests. This book is an account of the proceedings, including appreciations of each paper and summaries of the ensuing discussion.

Unfortunately, many of the contributions were long on homespun philosophy and short on facts, so that the clinician looking for useful information will be disappointed.

There were exceptions. Savarese and Ali presented an excellent review of neuromuscular monitoring, with proposals for standardized recording conditions; Dauchot considered in depth the possible uses of systolic time intervals, and Ty Smith gave a useful over-view of developing trends in computer-aided e.e.g. monitoring. Even these contributions are now a little dated, because of the 2-year delay in publication.

The chapter on "Legal Aspects" made me glad to be in England.

C. J. Hull

Diabetes Mellitus. By M. I. Drury. Published (1979) by Blackwell Scientific Publications, Oxford, London, Edinburgh. Pp. 125; indexed. Price £3.50.

The author, who is physician in charge of the Diabetes and Endocrine Unit of the Mater Misericordiae Hospital, Dublin, stresses that this book is intended as a short source of background information for the general physician and specialists in other fields.

The opening three chapters summarize current thinking as to the aetiology, classification and diagnosis of diabetes in such a way that the non-endocrinologist can understand. This is followed by a chapter which lists all the hypoglycaemic drugs and forms of insulin which are available; there are details of half-life, onset of action etc. Important drug interactions are also discussed.

The chapters on vascular changes and skin and hand disorders will show readers the difficulties facing the expert in diabetes in carrying out his everyday work. The management of diabetes in pregnancy and in childhood are best managed by the experts, but this book contains guidance which is helpful and points to the need for co-operation between obstetricians, anaesthetists and neonatologists.

While each chapter has a list of references for further reading, it would be helpful to include the works of authors mentioned in the text. Those working in the field of diabetes are undoubtedly familiar with the large number of abbreviations used (GCT, JDD, SAA, NLA etc.). Although these are defined when first mentioned, it would be helpful to have a comprehensive list.

The book is attractively produced with clear print and a simple style of writing, both easy to read. At £3.50 it is good value for money.

J. W. Dundee
M. P. O'Neill

Practical Anesthetic Pharmacology. Edited by Rafik R. Attia and Alan W. Grogono. Published (1978) by Appleton-Century-Crofts, New York. Pp. 293; illustrated; indexed. Price £12.90.

It is difficult to imagine that many British anaesthetists will find this book of use. This is a pity, since the aims of the editors are to provide a compact pharmacology text for trainees and practitioners in anaesthesia. The text consists of concise pharmacological descriptions followed by many tables of facts, so that readers might quickly refresh their memories about a subject or drug. This makes the book too tedious to read for pleasure and even as a last-minute read for examinations it fails on several points.

First of all, it is almost entirely American, with little or no attempt to describe drugs which are available in the U.K. but not in America, for example lorazepam, buprenorphine, metoclopramide and etomidate. Other aspects of this flaw, such as describing cylinder colour codes only according to the American system and using entirely American approved names without the British names even in parentheses, are annoying for the British reader. A more serious flaw, however, is the relative allocation of importance to different groups of drugs. For example, i.v. anaesthetic agents are dealt with very briefly, in less than six pages, while anticoagulants receive more than eight pages. The table of facts about vitamins is much larger and more comprehensive than that for i.v. anaesthetic agents.

Only two chapters (Local Anaesthetic Agents, and Drug and Disease Interactions) contain references; the others have a bibliography. In the chapter on analgesia, although some statements have numbers to represent references, these do not appear at the end of the chapter. There are a few inaccuracies, for example naloxone's effects last for as long as 4 h, and others in the section on anti-inflammatory drugs.

The section on local anaesthetic agents by Dr Covino is excellent and the chapters on neuromuscular blockade and drug and disease interactions are very good. The Appendix contains much information which appears irrelevant to the title of the book, but the index is good and the book is clearly laid out.

Walter S. Nimmo

Printed in Great Britain by John Wright and Sons Ltd. at The Stonebridge Press, Bristol BS4 5NU

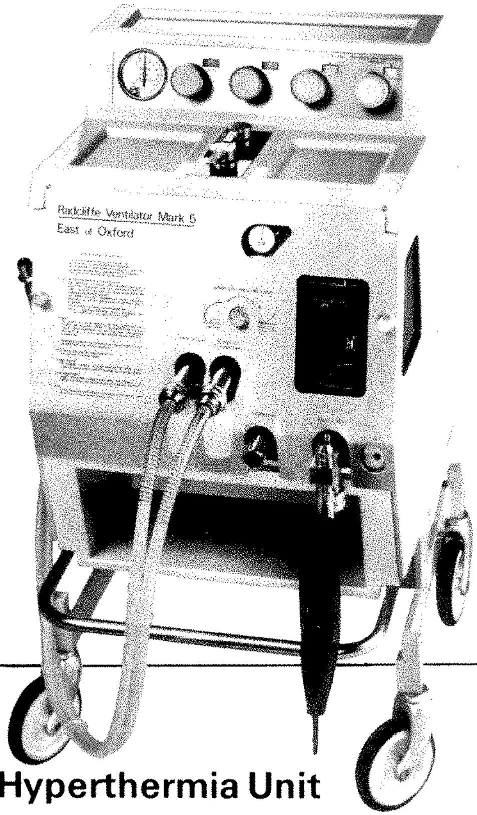
© Macmillan Journals Ltd 1980

EAST OF OXFORD

...is a name known throughout the world for advanced and reliable electro-mechanical anaesthetic apparatus.

The East-Radcliffe Mk. 5 Ventilator

The latest model in a well-proven series – reliable and simple to operate. Autoclavable patient circuitry. Variable respiration rate. The unit may be used as a time-cycled pressure generator or as a volume-limited ventilator.

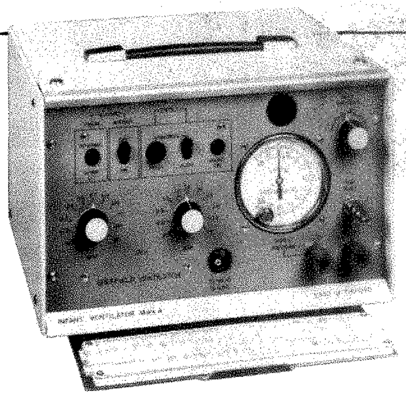


Hyperthermia Unit

This controlled water temperature unit will supply warm or cool water to a blanket within the 4°C to 40°C range. Readily portable, quiet, corrosion proof and reliable.

Humidifier Unit

East's blower-assisted humidifier unit provides a steady stream of warm, saturated air or oxygen for spontaneously breathing patients using tracheostomy boxes.



Sheffield Infant Ventilator Mk. 4

For anaesthesia or long-term ventilation of infants up to the age of three, the Mk. 4 unit is time-cycled, volume-controlled and pressure-limited with a wide range of respiratory rates.

East-Freeman Ventilator

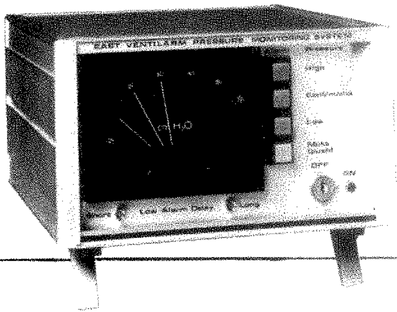
Suitable for long or short-term use in ward or intensive care units – or in the operating theatre for controlled/assisted ventilation with anaesthetic gases

East-Radcliffe Respirator

A highly compact theatre trolley unit which can supply anaesthetic gases by hand or automatically. The unit will also function as a ward ventilator.

The East Ventilarm Pressure Monitor/Alarm System

The East Ventilarm provides maximum protection to a patient connected to a lung ventilator and is activated by any change in the pressure pattern.



H.G. EAST & COMPANY LTD.
Littlemore, Oxford. OX4 5JT. Tel: Oxford 779361
A subsidiary of British Syphon Industries Ltd

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 2 *Published monthly* FEBRUARY 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27.50, Airmail £50 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

CONTENTS

PAGE

EDITORIAL: Muscle 109
F. R. Ellis and J. Norman

SYMPOSIUM ON MUSCLE

The physiology of striated muscle 111
K. Floyd

Muscle biochemistry 123
J. A. Illingworth

Pathology of muscle 139
P. H. Buxton

Inherited muscle disease 153
F. R. Ellis

Malignant hyperthermia—pearls out of swine? .. 165
G. M. Hall, J. N. Lucke and D. Lister

Neuromuscular pharmacology. *A clinical update and commentary* 173
C. Lee and R. L. Katz

EXPERIMENTAL

Minimum artificial lung expansion necessary for resuscitation of the newborn lamb 189
R. S. Vaughan, W. W. Mapleson, M. Rosen and K. M. Laurence

Effect of acute hypocapnia on renal function in the dog artificially ventilated with nitrous oxide, oxygen and halothane 197
J. M. Hunter, R. S. Jones and J. E. Utting

Effects of anaesthetics on guineapig tracheal smooth muscle 199
F. Okumura and M. A. Denborough

CLINICAL INVESTIGATION

Maturation of neuromuscular transmission in the infant 205
N. G. Goudsouzian

PAGE

Postoperative muscle pains and suxamethonium 215
J. B. Brodsky and J. Ehrenwerth

Enflurane in outpatient paediatric dental anaesthesia. A comparison with halothane 219
R. H. A. Hoyal, C. Prys-Roberts and P. J. Simpson

Adverse effects of buffered glutaraldehyde on the Heidbrink expiratory valve 223
S. M. Mostafa

ABSTRACTS

Proceedings of the Anaesthetic Research Society, London Meeting, November 23, 1979 .. 229P

CORRESPONDENCE

Consciousness during anaesthesia 241
Extradural space 241
Pharmacokinetics of minaxolone 241
Inefficiency of antacid in prevention of aspiration pneumonia 241
I.v. equipment design and infection 242
Delayed blockage in an extradural catheter .. 242

BOOK REVIEWS

Outpatient Anaesthesia 243
Dangerous Mistakes in Drug Administration: 1979 243
Clinical Pharmacology: Basic Principles in Therapeutics 243
Monitoring Patients in The Operating Room .. 244
Diabetes Mellitus 244
Practical Anaesthetic Pharmacology 244

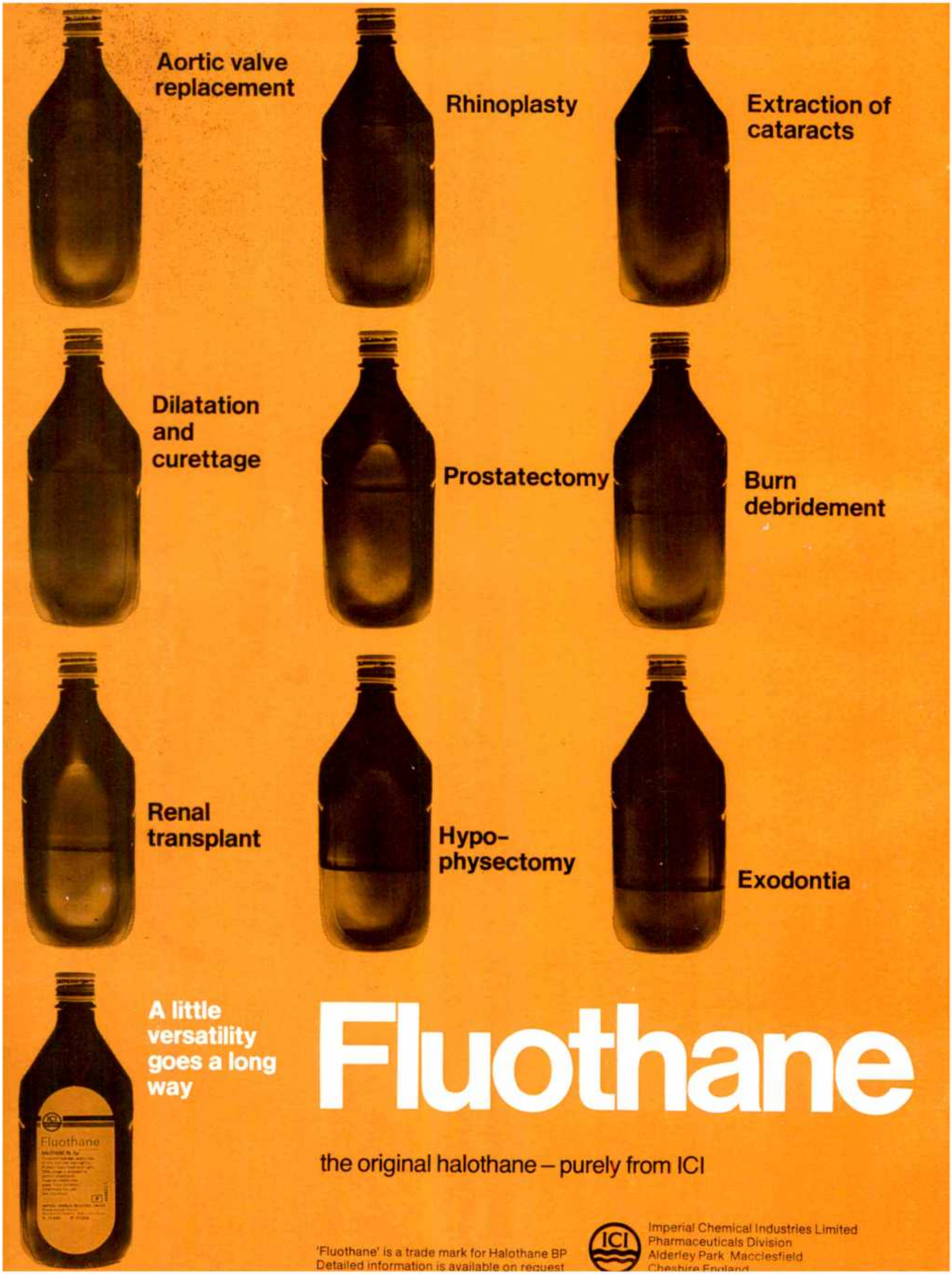
EDITORIAL BOARD page ii

MACMILLAN JOURNALS LTD, 4 LITTLE ESSEX STREET, LONDON WC2R 3LF

Volume 52, No. 3 March 1980

British Journal of Anaesthesia

Editor of General Issues: A. A. Spence



'Fluothane' is a trade mark for Halothane BP
Detailed information is available on request

Imperial Chemical Industries Limited
Pharmaceuticals Division
Alderley Park Macclesfield
Cheshire England

The gentlest touch

The delicate tissue lining of the trachea needs the gentlest possible handling during intubation. That's why Searle have developed Sensiv, the ultra low pressure endotracheal tube:

- *Thin walled pre-formed cuff designed for unprecedented compliance*
- *Ultra low intracuff pressure remains below acceptable maximum even after long periods of anaesthesia*
- *No wrinkles formed on inflation—aspiration prevented.*

New **Sensiv**

Low pressure cuff endotracheal tube

Please return this coupon to:

Searle Medical Products,
Division of G. D. Searle & Co. Ltd.,
P.O. Box 88, Lane End Road,
High Wycombe, Bucks.

SEARLE

Please send me a sample and detailed information on Sensiv.

*Name*____________________

*Position*____________________

*Address*____________________

BA 9673A

LIBRARY

EDITORIAL BOARD

Editor of General Issues

A. A. SPENCE, *Reader, University Department of Anaesthesia, Western Infirmary, Glasgow*

Editor of Postgraduate Educational Issues

J. NORMAN, *Professor of Anaesthetics, The General Hospital, Tremona Road, Southampton SO9 4XY*

C. M. CONWAY, *Professor of Anaesthesia, Westminster Hospital, London*
E. A. COOPER, *Professor of Anaesthesia, University of Newcastle upon Tyne; Honorary Consultant Anaesthetist, Newcastle University Hospitals*
J. W. DUNDEE, *Professor of Anaesthesia, Queen's University of Belfast*
F. R. ELLIS, *Reader in Anaesthesia, University of Leeds*
W. FITCH (Assistant Editor), *Senior Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*
G. M. HALL, *Senior Lecturer in Anaesthetics, University of London, Royal Postgraduate Medical School*
C. J. HULL, *Senior Lecturer in Anaesthesia, University of Newcastle*
A. R. HUNTER (Chairman), *Professor of Anaesthesia, University of Manchester*
D. G. MCDOWALL, *Professor of Anaesthesia, University of Leeds*
W. W. MAPLESON, *Professor of the Physics of Anaesthesia, Welsh National School of Medicine, University of Wales*
J. F. NUNN, *Head of Division of Anaesthesia, Clinical Research Centre, Harrow; Honorary Consultant Anaesthetist, Northwick Park Hospital*
J. P. PAYNE, *British Oxygen Research Professor of Anaesthetics, Royal College of Surgeons of England*
C. PRYS-ROBERTS, *Professor of Anaesthetics, University of Bristol*
J. E. RIDING (Hon. Treasurer), *Consultant Anaesthetist, United Liverpool Hospitals; Honorary Lecturer in the Department of Anaesthesia, University of Liverpool*
J. G. ROBSON, C.B.E. *Professor of Anaesthetics, University of London, Royal Postgraduate Medical School*
D. B. SCOTT, *Consultant Anaesthetist, Royal Infirmary Edinburgh*
G. SMITH, *Professor of Anaesthesia, The General Hospital, Leicester*
M. K. SYKES, *Professor of Clinical Anaesthesia, Royal Postgraduate Medical School, London*

Editorial Assistants

KIRSTEEN M. S. DEWAR, *Consultant Anaesthetist, Western Infirmary, Glasgow*
G. N. C. KENNY, *Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*

Papers for publication and all editorial communications should be addressed to the Editor, University of Glasgow, Department of Anaesthesia, Western Infirmary, Glasgow G11 6NT; business communications to the publishers: Macmillan Journals Ltd, 4 Little Essex Street, London WC2R 3LF.

The GUIDE TO CONTRIBUTORS can be found on pages x, xii & xiv of the advertisement section of this issue.

Published monthly. Annual subscriptions: U.K. £22·50, U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27·50, Airmail £50; (or equivalent in any other currency). ISSN 0007-0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.

Overseas subscribers may make payments into U.K. Post Office Giro Account No. 519 2455. Full details must accompany the payment.

Second Class Postage Paid New York, N.Y. U.S. Mailing Agent: Expediters of the Printed Word, Ltd, PO Box 1305, Long Island City, N.Y. 11101.

All enquiries concerning advertising should be addressed to Advertisement Department, Macmillan Journals Ltd, 3 Dyers Buildings, Holborn, EC1N 2NR (Telephone 01-831 6901). © Copyright: Macmillan Journals Ltd, 1980.

12.9.80

Regional Anaesthesia Update 1980

International Symposium
Heidelberg, W. Germany
September 22-25, 1980

Sponsored by
American Society of Regional Anesthesia
German Society of Anaesthesia and Intensive Care Medicine

Invited Faculty:

E. Armitage
H. Bergmann
R. Boas
J. Bonica
D. Bridenbaugh
P. Bridenbaugh
P. Bromage
H. Carron
B. Covino
S. Crawford
R. DeJong
M. Finster
A. Hollman
J. Katz
B. Löfström
P. Lund
D. Moore
H. Niesel
H. Nolte
G. Ostheimer
P. Raj
S. Shnider
O.H. Schulte-Steinberg
B. Scott
D. Selander
M. Stanton-Hicks
M. Swerdlow
A. Winnie

Topics:

Local Anesthesia
Surgical Regional Anesthesia
Obstetrical Regional Anesthesia
Regional Anesthesia for Pain Control

World Federation of Societies of Anesthesiologists
precedes Symposium in Hamburg, G.F.R., Sept. 14-21, 1980

Regional Anaesthesia Update 1980

International Symposium
Heidelberg, W. Germany
September 22-25, 1980

For Information, mail to:

P.P. Raj, M.D.
P.O. Box 11083
Richmond, Va. 23230, USA

Hans Nolte, M.D.
Institut Für Anaesthesiologie
4950 Minden, West., G.F.R.

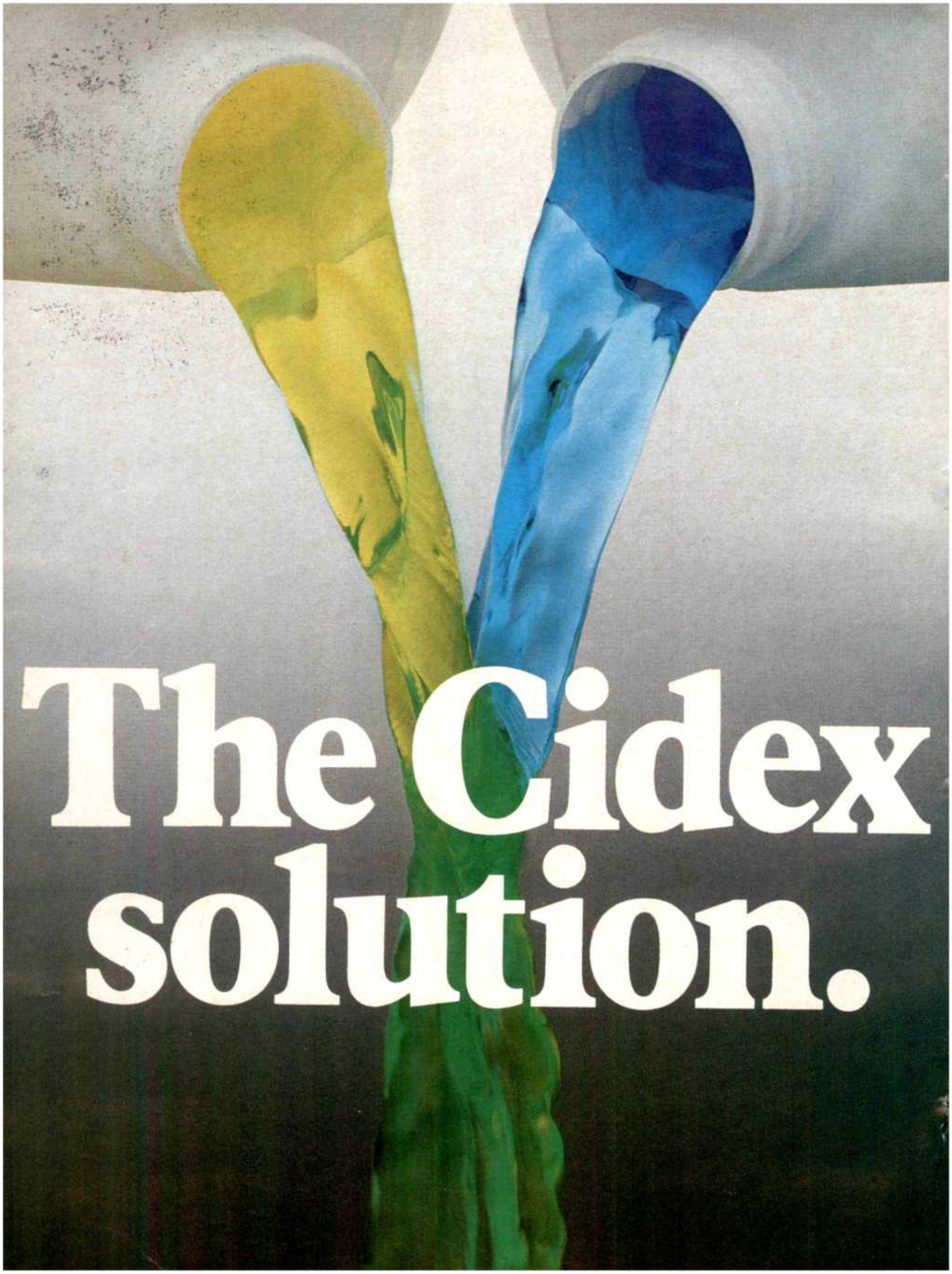
(PLEASE PRINT)

Name ____________________

Address ____________________

City/State/Zip/Country ____________________

☐ ASRA Member ☐ Send ASRA Membership Information


The Cidex solution.

It has long been recognised that different hospitals have different disinfection and sterilization requirements.

These differences, of course, arise from the degree of contamination present, the type of equipment and rate of throughput, and the cleaning/drying procedures used.

What hasn't been recognised sufficiently up till now is that these factors combine to have a cumulative effect on the use-life of cold disinfectant solutions–creating a need for solutions with different use-lives.

To meet this need there are now two solutions.

–CIDEX* Activated Glutaraldehyde Solution with a use-life of up to 14 days.

–CIDEX* Long-Life Activated Glutaraldehyde Solution with a use-life of up to 28 days.

New CIDEX* Long-Life Solution has all the trusted and well-proven benefits of 14 day CIDEX* Solution but has an effective life of 28 days where usage factors permit.

A fresh peppermint odour and blue colour differentiate CIDEX* Long-Life from green 14 day CIDEX* Solution.

WHICH CIDEX* SOLUTION TO USE

While the effects of dilution and gross protein contamination are always present, these can be minimal due to low throughput.

Under these circumstances, new CIDEX* Long-Life Solution is much more convenient and can offer substantial cost savings.

In a busy unit, however, where pressures generally do not permit drying, protein contamination and dilution can build up over a period–particularly with bulky items, such as anaesthetic tubing, which have a high carry-over of water.

In situations such as this, 14 day CIDEX* Solution offers complete assurance of its efficacy, assurance which has been confirmed repeatedly all over the world.

CIDEX* SOLUTIONS. NOT ONLY A CHOICE BUT A BETTER CHOICE

Both solutions have the complete range of cidal activity which has made CIDEX* Solution the prime agent of choice for disinfection and sterilization of heat sensitive and delicate equipment.

Both have the remarkable non-corrosive properties which in laboratory tests have proven them to be less corrosive than deionised water.

14 day CIDEX* Solution in the green container. 28 day CIDEX* Long-Life Solution in the blue container.

Whatever your choice, you can be confident that CIDEX* is the safest, most cost-effective solution to your disinfecting or sterilizing problem.

A choice of CIDEX* solutions from Arbrook–now you can choose wisely.

Arbrook*

Arbrook Products Limited, Livingston, Scotland EH54 7AT *Regd. Trademark © Arbrook Products Limited 1979.

You've worked hard for your money

-now let it work hard for you.

Like you, we at Lombard rely on our hard earned skills. Our experience over many years has made us an important name in British Banking and Finance to help people like you make their money grow by depositing with us.

We have a wide range of specially designed Deposit Account Schemes offering sound rates of interest which is paid without deduction of tax at source.

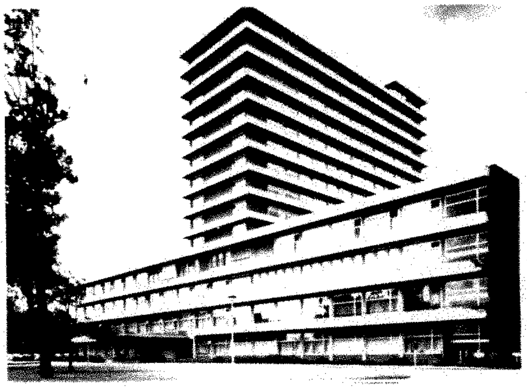
For further details of our deposit facilities and current interest rates without any obligation, simply post the coupon today.

Lombard North Central
Bankers

To:
LOMBARD NORTH CENTRAL LTD,
DEPT. U942,
17 BRUTON STREET,
LONDON W1A 3DH.
Tel: 491 7050

Name:
(BLOCK CAPITALS PLEASE)
Address:

A member of the National Westminster Bank Group whose capital and reserves exceed £1,300,000,000.



ELISABETH-KRANKENHAUS RHEYDT

4050 Monchengladbach 2

—Schwerpunktkrankenhaus mit 8 Fachdisziplinen und über 500 Betten sowie einer Belegabteilung mit 130 Betten—

sucht zum nächstmöglichen Eintrittstermin für die Anästhesieabteilung (Chefärztin Dr. med. Schäffer)

1 ersten Oberarzt (-ärztin)

und

1 Assistenzarzt (-ärztin)

Die Anästhesieabteilung, der eine modern eingerichtete Intensivstation angeschlossen ist, betreut alle operativen Kliniken (Chirurgie, Gynäkologie, Urologie, HNO/Augen und die angeschlossene Belegabteilung).

Es kommen alle Anästhesieverfahren einschl. der grossen regionalen Anästhesien (Spinal, PDA, Kaudale, Sattelblock, Plexus und die verschiedensten Nervenblockaden) zur Anwendung.

Die Chefärztin ist zur vollen Weiterbildung ermächtigt.

Geboten werden:

- Anstellung wie im öffentlichen Dienst
- Vergütung nach BAT sowie alle Sozialleistungen des öffentlichen Dienstes (Beihilfen, zusätzliche Altersversorgung usw.)
- Bereitschaftsdienstvergütung/Rufdienstvergütung
- Nebeneinnahmen aus Zuwendungen des Chefarztes
- Trennungsentschädigung, Umzugskostenvergütung
- moderne Einzelzimmer zu günstigen Bedingungen bzw. Unterstützung bei der Wohnraumbeschaffung

Bewerbungen mit den üblichen Unterlagen werden erbeten an

ELISABETH-KRANKENHAUS RHEYDT
Postfach 186, 4050 Mönchengladbach 2,
Tel. (02166) 3511

Universal Tube Holder

From Downs Surgical.

British Patent No 1 471 609
Designed by Laurence F Tinckler MD, ChM, FRCS, FACS.

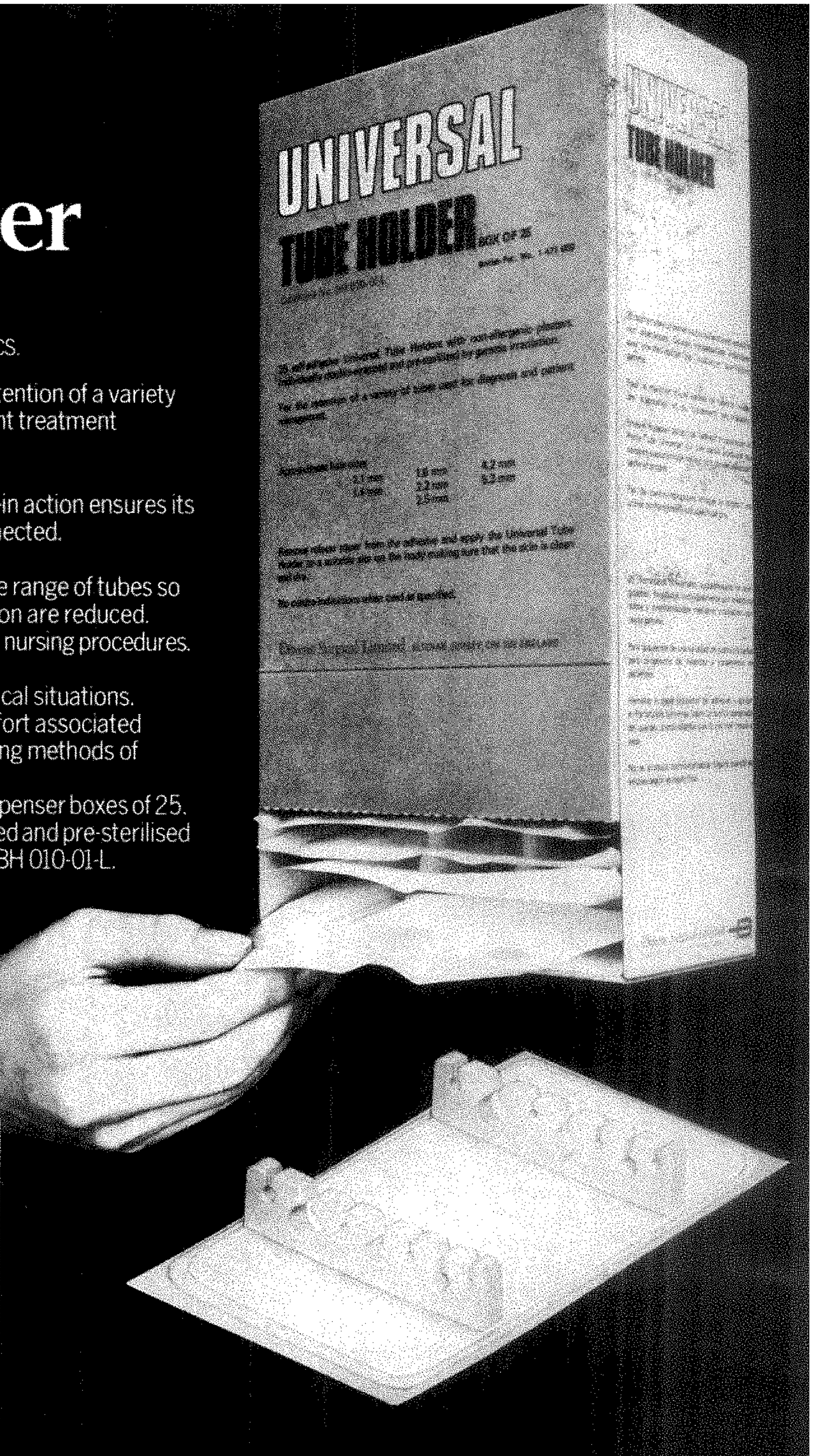
For the fast, convenient and comfortable retention of a variety of tubes, catheters and leads used for patient treatment and diagnosis.

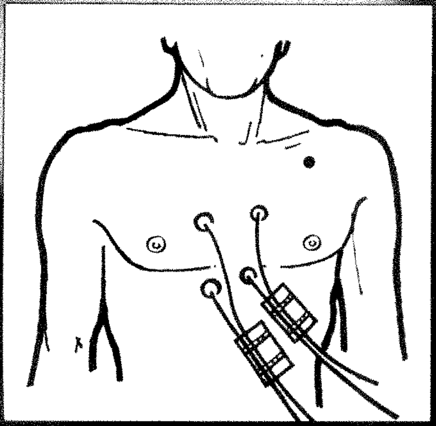
☐ **Fast:**
May be positioned immediately. Unique slot-in action ensures its easy application after tubes have been connected.

☐ **Convenient:**
Seven different slot sizes for retaining a wide range of tubes so that the risks of tension, kinking and occlusion are reduced. Tubes can be temporarily released to facilitate nursing procedures.

☐ **Comfortable:**
The flexible base conforms to most anatomical situations. Non-allergenic adhesive. Avoids the discomfort associated with bandages, strapping and anchor-suturing methods of tube retention.

The Universal Tube Holder is packaged in dispenser boxes of 25. Each Universal Tube Holder is double-wrapped and pre-sterilised by gamma irradiation. Catalogue reference BH 010-01-L.





Downs Surgical - simply the best

To: Disposable Products Division, Downs Surgical Limited, Church Path, Mitcham, Surrey, CR4 3UE, England.
Please send me further information and samples of the Universal Tube Holder.

Name & Title ________ Date ________ Position ________

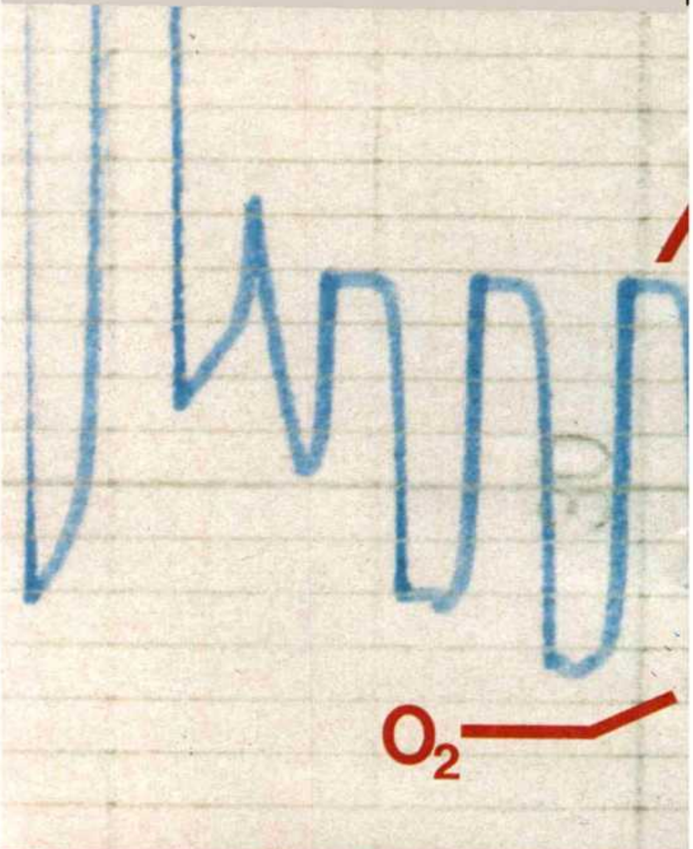
Address ________ Post Code ________

Up to four blood gases examined and compared continuously and virtually simultaneously, using one miniature probe and without withdrawing a single drop of blood.

It's the work of the new Medishield Multi-gas Transcutaneous Probe – a remarkable advance in non-invasive blood gas monitoring.

The simple, semi-disposable probe assembly and temperature controller come as a low-cost accessory to the Medishield Multi-gas Monitor MS2.

Multi-gas
Monitor
MS2



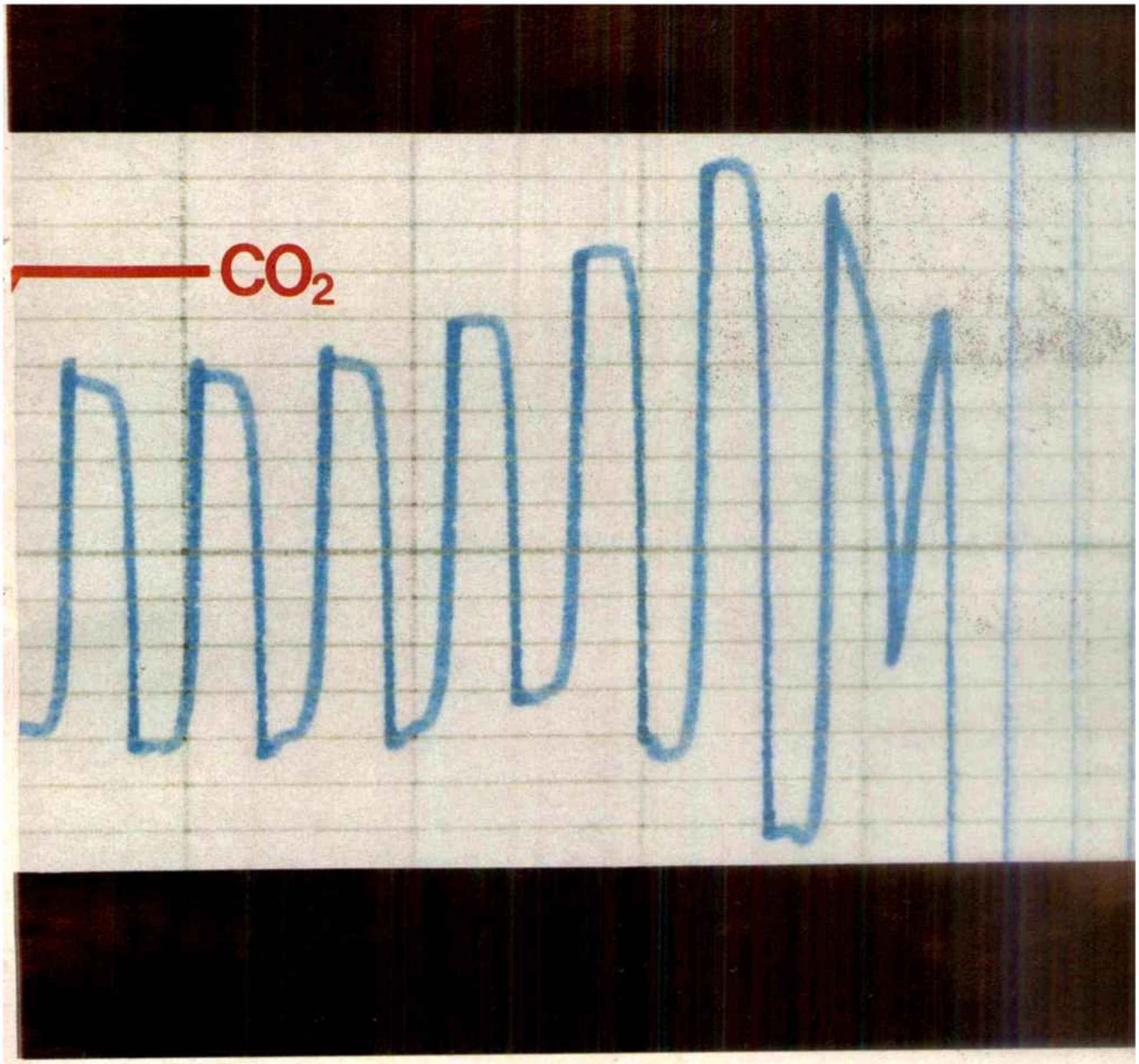
Using advanced mass spectrometry techniques, the equipment is able to process the tiniest samples of transcutaneous gas diffusing from a heated skin area of only 0·5 cm.^{2}

There has never been a more acceptable method of comprehensively monitoring blood gas levels in intensive care.

Medishield

Cyprane
New Devonshire House, Scott Street,
Keighley, W Yorks BD21 2NN
Tel: Keighley (0535) 67811 Telex: 51631
Part of the Medishield Corporation

The Medishield Multi-gas Transcutaneous Probe
The first non-invasive, multi-gas



...and we never touched a drop

GUIDE TO CONTRIBUTORS

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. Two issues each year deal mainly with material of postgraduate educational value.

PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publishers.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted.

LEGAL CONSIDERATIONS

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

PREPARATION OF MANUSCRIPT

Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full addresses) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headded)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

Title page

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should also be suggested.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the experiments to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of experimental results, while concise, should permit repetition of the experiments by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of

This Handbook is an essential reference for anaesthetists and those associated with the speciality.

Designed to provide factual and commercial information of value to departments of Anaesthesia in their dealings with other organisations and to those wishing to commence the practice of anaesthesia as a training.

Handbook of British Anaesthesia 1979/80

Contents include comprehensive information on:

National and International bodies in Anaesthesia
National specialist societies
Regional and local societies
University departments of anaesthesia
National Health Service Postgraduate Training areas
and National Health Service Advisory and Consultative machinery

Published price of the Handbook is £5.95 but there is a special price to subscribers of the journal. For information write to:
Frances Roach, Scientific and Medical Division, Macmillan Publishers Ltd, Publishing Building, Houndmills, Basingstoke RG21 2XS, England.

digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

Discussion

The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially.

References

There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

In the case of books, the reference should be as follows: name of author and initials; year of publication in parentheses; title of book, underlined; number of edition; page number; town of origin, publisher; for example: Hill, D. W. (1971). *Physics Applied to Anaesthesia*, 2nd edn, p. 212. London: Butterworths.

The *British Journal of Anaesthesia* should be referred to as *Br. J. Anaesth.*

In the text up to three authors should be named before the use of ". . . et al.". If reference is made to several publications during a particular year, written by a larger group of authors who have alternated the order of authorship, as many names must be written as are necessary to distinguish between the publications, before use of ". . . et al." in conjunction with the year suffixes a, b, c.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase "(in press)" replacing volume and page number.

It is essential that authors verify the content and details of references which they list, as this responsibility cannot be accepted by either Editors or Publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ ◐
◑ ◒ ⊙ ☉ ⦶ ⊕ ⊖ ▩ ■ ▤ × +

The name of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It is emphasized that care taken in the original preparation of figures will obviate the time-consuming and expensive necessity of their revision.

Patients are quick to sit up and take notice after

ALTHESIN

(alphaxalone and alphadolone acetate)

the anaesthetic for short procedures

Recovery is outstandingly good, rapid and progressive

"Althesin appears to be an excellent induction agent."[1]

Althesin provides a rapid and pleasant recovery with a low incidence of hangover.[1]

Patient acceptance is high and the incidence of nausea and vomiting is low.[2]

"Patients from morning lists are quite able to have a full lunch, which they could not have done with any barbiturate."[3]

1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

Glaxo

Glaxo Laboratories Limited
Greenford, Middlesex
UB6 0HE

Althesin is a Glaxo trade mark

Uses
Induction of anaesthesia.
Maintenance of anaesthesia.
Experience is insufficient at present to advocate use of Althesin in infants under one year, in patients with hepatic dysfunction, and for maintenance of anaesthesia in obstetrics.

Dosage and administration
As usual, it is recommended that patients should fast before receiving Althesin.
The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e., half to three-quarters of a millilitre per 10kg.
Younger children usually require the higher dose and may need 0·075ml/kg bodyweight. Althesin should be injected slowly, taking no less than 30 seconds, as this promotes smooth induction.
Althesin has negligible analgesic activity.

Contra-indications
Previous adverse reactions to Althesin.
Hepatic failure.

Precautions
Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants of the central nervous system may retard recovery of full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume normal activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects
Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, and of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post-operative nausea and vomiting are infrequent. There have been occasional reports of more severe reactions. Bronchospasm and/or a marked drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids and plasma expanders.

Overdosage
If serious respiratory depression occurs, respiration should be supported mechanically. The margin of safety is wide, and 0·2ml/kg, or four times the minimum sleep dose, has been given as a single dose without serious effects.

Packs
Ceramically-printed 5 or 10ml ampoules in boxes of 10 ampoules.

Product Licence number 4/0189
Price to Hospital (exclusive of VAT)
5ml 80p

General information

Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available:

1.	PART I	(capitals)
2.	RESULTS	(small capitals)
3.	Blood-gas analysis	(l.c. roman)
4.	*The action of drugs*	(italics, centre)
5.	*Lung function studies*	(italics, full out)
6.	*Volume.* Large volumes. . . .	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet "Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors" (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

CORRESPONDENCE

It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

PROOFS

These should be corrected and returned to the sub-editor *within 48 hours of receipt.* Overseas contributors should return their proofs by airmail.

REPRINTS

Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

ORGANON TEKNIKA INFORMATION SERVICE

Neuromuscular Transmission & Anaesthetic Agents

This quarterly pocket edition is intended as a convenient aid to the anaesthetist interested in current progress with neuromuscular transmission and drugs.

Each edition carries a special feature, a bibliography of current publications concerning anaesthetic agents and a suggested list of further reading. The information is elicited from 27 current journals.

If you would like to receive a copy regularly or copies of previous editions please contact:

ORGANON TEKNIKA

Organon Teknika Limited, Teknika House,
Cromwell Road, St. Neots,
Cambridgeshire. PE19 2HS

Tel. No. Huntingdon (0480) 76963

A service from the manufacturers and distributors of Pavulon pancuronium bromide – the muscle relaxant of choice

When seconds count...

the MA-2 can be a lifesaver.

When a patient suddenly fails to breathe spontaneously during IMV or CPAP procedures, time can be critical. Simple warning systems may prove inadequate. The MA-2 with its unique Fail-to-Cycle switchover mechanism not only warns the operator, but also automatically switches the MA-2 to a mandatory ventilation mode and controls the patient's ventilation at levels preselected by the operator until help arrives. Those additional precious seconds of mandatory ventilation that only the MA-2 can provide may prove to be a lifesaver.

So buy the best... Buy Puritan-Bennett.

Puritan-Bennett International Corp.
Bognor Road, Chichester, Sussex PO19 2PH.
Telex: 86462. Cables: Puremade Chichester.
Serving Europe, the Middle East and Africa

PURITAN-BENNETT
CORPORATION

10th & Harrison, Berkeley, California 94710.
Serving Japan, Australia, the Philippines, India and the Pacific Orient
7280 N.W. 58th Street, Miami, Florida 33166.
Serving Central America, South America, Mexico and the Caribbean

THE ACCUROX**
OXYGEN MASK.
MORE AND MORE
PEOPLE ARE COMING
ROUND TO IT.

"It was found that patients left the ACCUROX** mask in position more frequently than the other…masks, and the Recovery staff did not have to keep replacing it due to the patient having rejected it in their post anaesthetic state."

"…INSPIRON** ACCUROX** masks..(have given).. considerable financial saving, high patient acceptability and reduction in storage space by standardisation on one mask."

Re-cycling oxygen masks in the Recovery Room.
N. Duffin - Nursing Times - 11th May 1978

For further details contact:-

Inspiron**

A Division of C. R. Bard International Limited
Pennywell Industrial Estate, Sunderland SR4 9EW
Tel: 0783 243131

**Trademark

Der Anaesthesist

The organ of the
Austrian, German and Swiss Societies
of Anaesthesiology and Reanimation

Edited by: A. Doenicke, München; R. Frey, Mainz; O. Mayrhofer, Wein; H. Schaer, Männedorf
Managing Editor: A. Doenicke, München, Chirurgische Universitäts-Poliklivik, Anaesthesie. Pettenkoferstr. 8a, D-8000, München 2

Contents DECEMBER 1979

U. Ottermann, R. Dudziak, E. Appel, D. Palm — The effect of hypothermia and methoxyflurane-anaesthesia on sympatho-neuronal and sympatho-adrenal activity in the course of cardiac surgery 551

K. Huse, H. Wiecken — Circulatory changes in the sitting position during neuorsurgical anaesthesia (NLA) 557

A. Csongrady, E. Mayr, H.-D. Kamp, H.-J. Volkholz — Dosage-Problems in controlled sodium nitroprusside hypotension in oto-rhino-laryngological surgery 564

S. Fitzal, E. Knapp-Groll, W. Ilias, W. Scherzer, L. Tonczar — A comparison of two preoperative medications: responses in sedative, psychic and somatic effects 572

A. Doenicke, J. Kugler, M. Kropp, M. Laub, G. Kalbfleisch — The hypnotic effect of the new benzodiazepine derivative lormetazepam when given introvenously 578

Th. Wallenfang, U. Mielke, J. Bohl, H. Bierbach — Local myocardial necrosis and cardiac tamponade due to a central venous catheter 584

Annual subscription: DM 180 + postage

Published by SPRINGER-VERLAG · Berlin · Heidelberg · New York

CANADIAN ANAESTHETISTS' SOCIETY
JOURNAL

Editor
R. A. GORDON
Assistant Editor: GORDON WYANT
Editorial Board
MARCEL BOULANGER A. W. CONN DOUGLAS B. CRAIG
KENNETH M. LEIGHTON EMERSON MOFFITT R. A. MELOCHE BERNARD PAIEMENT

The Journal is issued bi-monthly for members of the Society and Subscribers. It contains original articles and reviews on clinical and basic science subjects related to Anaesthesia.

Annual Subscription $30.00 post paid
First Class Airmail $12.00 extra (optional).
The Secretary
Canadian Anaesthetists' Society
178 St. George Street, Toronto M5R 2M7, Ontario, Canada

The new IVAC 630 Volumetric Infusion Pump is surely accurate and it speaks for itself

With all the safety and accuracy you'd expect from IVAC, the new IVAC 630 is without doubt the most sophisticated infusion pump ever developed.

Its unique micro-computer makes drug and fluid delivery more trouble-free than ever before. It displays a wide variety of messages, from set-up procedures to alarm situations on its easy-to-read display panel. As a result, improper set-up is unlikely and the operator knows at a glance the total volume delivered, the exact flow rate and what problems there are should an alarm situation occur.

Designed to deliver fluids in a closed system within fine tolerances, the IVAC 630 is ideal for critical infusions requiring very high or very low rates. Furthermore, the volume infused is displayed in 0.1ml increments. So, send today for details about the first infusion pump to actually speak for itself. And let us talk to you.

IVAC
IVAC House, Bessborough Road,
Harrow, Middx. HA1 3DT.
Tel: (01) 864 9624. Telex: 8951734.

IVAC 630 Volumetric Infusion Pump

New self-regulating hygroscopic humidifier for anesthesia and intensive care

The Servo Humidifier, a new unique hygroscopic humidifier, is capable of maintaining 80% r.h. at 37 °C in the trachea of mechanically ventilated patients, receiving totally dry respiratory gases. A conventional heat and moisture exchanger, will maintain only 55% at 37 °C.

In most clinical applications the hygroscopic Servo Humidifier replaces the conventional bubble type, reservoir humidifier, thus eliminating the need for an external water and electrical supply.

The hygroscopic Servo Humidifier eliminates condensation in the patient tubing circuit and can be used with all mechanical ventilators and most anesthesia gas machines.

Contact your local Servo Ventilator distributor for our fullcolor Servo Humidifier folder and further information or write directly to us.

Servo Humidifier 150 and 151

I would like to have more information about the Servo Humidifier

Name

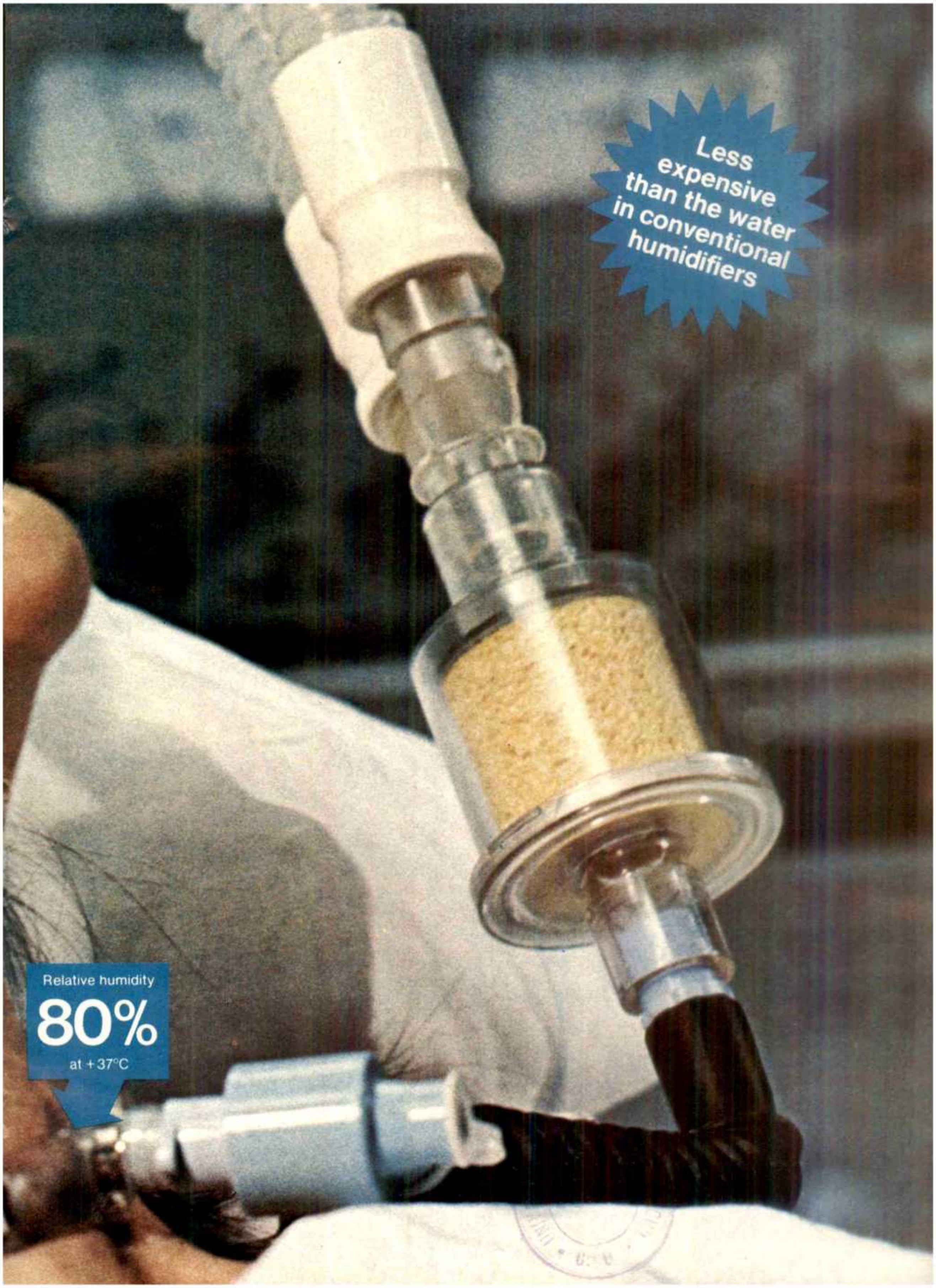
Position

Hospital

Address

SIEMENS-ELEMA
Siemens Limited, Medical Group, Siemens House
Windmill Road, Sunbury-on-Thames, Middlesex TW16 7HS
Telephone: (9327) 85691

For countries outside Great Britain:
Siemens-Elema AB, Ventilator Division, S-171 95 Solna, Sweden


Less expensive than the water in conventional humidifiers
Relative humidity
80%
at +37°C

September 14–21, 1980

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS
7th WORLD CONGRESS OF ANAESTHESIOLOGISTS
HAMBURG

Federal Republic of Germany

Deadline for submission of abstracts: January 31, 1980

Deadline for registration: May 31, 1980

Further information by:

Organizing Committee
7th World Congress of Anaesthesiologists
c/o Hamburg Messe and Congress GmbH
—Dept. for Congress Organisation—
P.O. Box 30 23 60. D-2000 Hamburg 36
Federal Republic of Germany

BRITISH MEDICAL
BULLETIN

Each Issue a Symposium on an Important Aspect of Contemporary Medical Research

VOL. 36, NO. 1 **JANUARY 1980**

CHEMICAL CARCINOGENESIS
Scientific Editor: *P. Brookes*

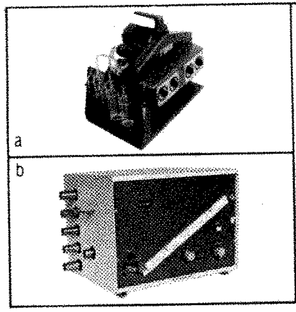
Introduction	*P. Brookes*
The history and future of chemical carcinogenesis	*E. Boyland*
The metabolic activation of chemical carcinogens	*Peter Sims*
DNA as a target of alkylating carcinogens	*P. D. Lawley*
Cellular responses to carcinogen-induced DNA damage and the role of DNA repair	*J. J. Roberts*
In-vivo–in-vitro analysis of ethylnitrosourea-induced brain carcinogenesis in the rat	*Joan P. Roscoe*
Multistage carcinogenesis in the urinary bladder	*R. M. Hicks*
Carcinogenesis by fungal products	*R. C. Garner*
Carcinogenesis and mineral fibres	*J. C. Wagner, G. Berry and F. D. Pooley*
Bacterial mutation as an indicator of carcinogenicity	*S. Venitt*
Carcinogenic synergism and its reflection *in vitro*	*John Ashby and J. A. Styles*
Interactions between carcinogens and proteins	*B. Ketterer*
Bracken fern and papilloma virus in bovine alimentary cancer	*W. F. H. Jarrett*
Antigenic changes in chemical carcinogenesis	*M. J. Embleton and R. W. Baldwin*
Bacterial metabolism and human carcinogenesis	*M. J. Hill*
Chemical carcinogenesis: whither epidemiology?	*Michael Alderson*

Price: UK, £6·00; Other countries, £7·20; USA and Canada, $15.00

Order from your local bookseller, or direct from

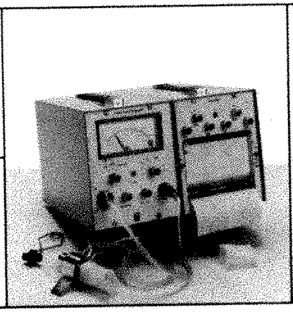
BRITISH MEDICAL BULLETIN
65 DAVIES STREET, LONDON W1Y 2AA

Gould Godart
The Pulmonary Care System Builders



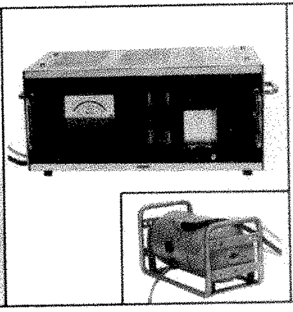
Gas mixing pumps and calibration set

a – simple solution for accurate/ reliable reproduction calibration/ clinical gas mixtures from pure gases.
– Extremely accurate.
b – Versatile monitoring and calibration of gas flow measurement equipment with ambient air.



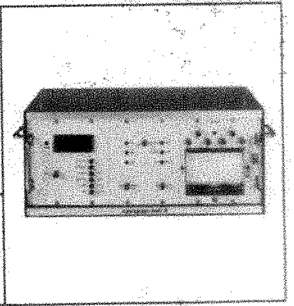
Pneumotachograph and Recorder

– Instantaneous measurement of respiratory gasflow with low breathing resistance.
– Essential respiratory parameters: $\dot{V}$ V, V_I + E, $V\Sigma 1$, MV, F, r.t.r., TV(Trend).
– Ten measuring ranges from 0-6 ml/s ro 0-15 1/S Computer compatable.



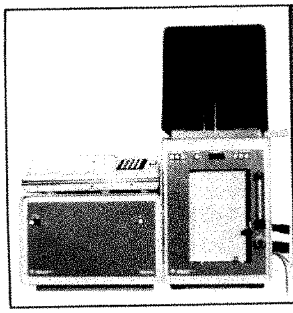
Rapox – O_2 Analyser

– Paramagnetic analyser.
– 2 measuring ranges: 21 to 11 vol% – 21 to 100 vol%.
– Non-sensitive to most anaesthetic gases.
– Rapid response 150 m/sec for 90%.
– Adjustable barometer pressure control.



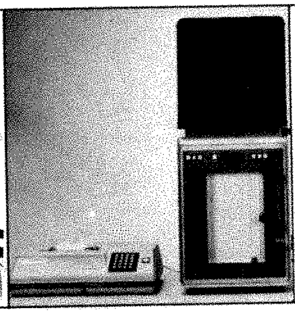
Capnograph Mark II I CO_2 Analyser

– Instant CO_2 analysis and respiration per min. measurement.
– Measures maximum expired CO_2 level and minimum inspired CO_2 level.
– Partial pressure readout or volume percentage.
– LED visual display window.



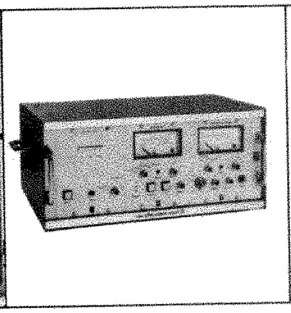
Diffumatic – single breath diffusion test unit

– Determines DLCO (SB) by closed circuit system for precise measurement control.
– Microprocessor controlled gas sampling system.
– Small pure CO gas bottle; replaceable and disposable.



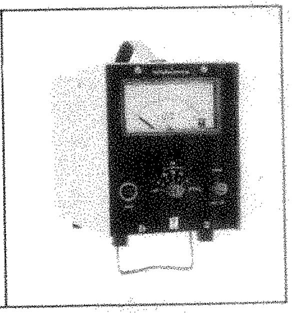
Pulmonet MK 3/Godamatic Computer/Printer

– Semi-automatic, self contained lung spirometer.
– Determines static, and dynamic lung, volumes.
– Expandable to complete lung function diagnostic centre.
– Automatic calculation and print-out of all pulmonary functions. 7 measurement parameters.



Compliance Test Mk 3

– A complete breathing mechanics measurement system.
– Combines presograph and pneumotachograph.
– Multi-purpose programmed module for $\dot{V}$ – V, P – V $\dot{V}$ – V + P – V From the P – V loop. Lung Compliance and Work of Breathing can be deduced.
– X-Y or X-YY recorder options.



The Godart Katapherometer

A rapid-response continuous gas analyser, capable of determining the dynamic measurements of helium and carbon dioxide present in inspired and expired respiratory gases.

Please forward to me further information on ______________ ______________ or tick ☐ if you wish to be contacted by us.

Name ______________

Address ______________

____

Position held ______________

Gould Medical UK, Main Street, Catthorpe, Nr Lutterworth,
Leics, England, Tel: Swinford (0788 85) 585.

The Gould Godart System Builders provide clinicians and researchers with a comprehensive range of state-of-the-art instruments designed to adapt to any specific pulmonary care situation instantly.
Combining electronic reliability and functional automation with mobility the System Builders require no specialist to operate. Swift and precise diagnosis is ensured.
For the full System Builder Story clip and mail the coupon.

Gould Medical UK, Main Street, Catthorpe,
Nr Lutterworth, Leics., England.
Tel Swinford (0788 85) 585.

GOULD

The choice is yours with the

PORTEX EPIDURAL SYSTEM

The most advanced design of Epidural Cannula* - smooth, flexible, kink-resistant, with excellent flow rates.

The Epidural Minipack - complete with the Portex Epidural Cannula** and thin-wall, single-use Tuohy needle - safe and economical with no costly extras.

The Portex Epidural Filter to complete the system, offering an effective bacterial and particulate barrier.

* Cannula supplied sterile in 16G and 18G, in radio-opaque or clear nylon. Option of 16G clear Cannula with open end.

** Minipack supplied sterile in 16G and 18G. Choice of radio-opaque or clear nylon Cannula.

For further details contact:

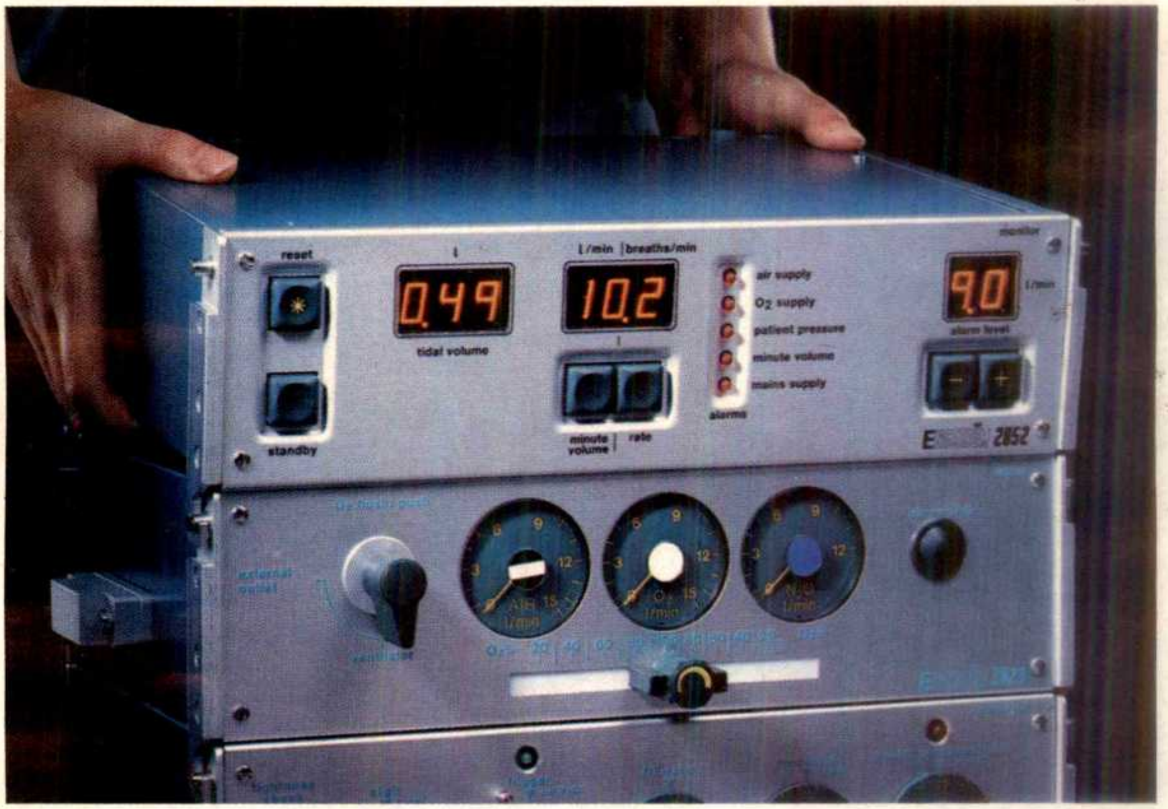
PORTEX LIMITED,
HYTHE, KENT, ENGLAND, CT21 6JL.
Tel: 66863 / 60551 Telex 96165

PORTEX S.A.,
ZI. de la VIGOGNE
62600 BERCK-SUR-MER,
FRANCE. Tel: (21) 090582

PORTEX

The Engström 2000 respirator with a brand new monitoring unit.

It can even print what's happening.



A new microprocessor controlled monitoring unit for the ventilation of the patient gives individual and easily-identified alarms that cover all situations. It gives you a digital display of breath-to-breath tidal volumes, true minute volumes, and the spontaneous or manual breathing rate.

The Engström 2000 is an electronic, modular design. It gives stable settings and has a wide choice of programmed functions, including PEEP, Trigger, Sigh, spontaneous breathing and manual ventilation.

A special feature is the printer output. A standard printer can give you a continuous printout of respiratory parameters and alarm conditions, if they occur. This printout, in plain words, is a unique Engström feature.

Your nearest Engström representative will be glad to give more information, or to arrange a demonstration.

ENGSTRÖM

Engström Medical AB,
Box 1295, S-17125 Solna, Sweden

Engström 2000 – the respirator with features that puts it ahead of all others.

ERRATUM

MASS SPECTROMETRY DURING CARDIOPULMONARY BYPASS

Br. J. Anaesth., **52**, 30 and 35

Equations (3) and (4) of the article by Dr Abbott and colleagues (p. 30) should read:

$$\dot{V}_{\mathrm{O_2}} = \dot{V}_{\mathrm{I}}\left(F_{\mathrm{I_{O_2}}} - \frac{F_{\mathrm{I_{TR}}}}{F_{\mathrm{E_{TR}}}} \cdot F_{\mathrm{E_{O_2}}}\right) \qquad (3)$$

$$\dot{V}_{\mathrm{CO_2}} = \dot{V}_{\mathrm{I}}\left(F_{\mathrm{I_{CO_2}}} - \frac{F_{\mathrm{I_{TR}}}}{F_{\mathrm{E_{TR}}}} \cdot F_{\mathrm{E_{CO_2}}}\right) \qquad (4)$$

The second sentence on p. 35 should read: . . . was maintained at 35 °C to 32 °C for 5 min . . .

SUBSCRIBE TO ANAESTHESIA & INTENSIVE CARE

Published quarterly by the Australian Society of Anaesthetists. Subscription rate 1980 $Aust.28.00. ($US33.00, £Stg.15), back issues/individual copies $Aust.7.00 ($US8.50, £Stg.4.50).

Please send your subscription request to: ANAESTHESIA AND INTENSIVE CARE,
P.O. BOX 525, POTTS POINT, N.S.W. 2011, AUSTRALIA.

Name ____________________

Address ____________________

____

Country ____________________ Code ____________________

Send no money at this stage. We will invoice you and commence your subscription with the current issue.

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 3 MARCH 1980

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement.

EDITORIAL

RELIEVING ACUTE PAIN

The research which led to the identification of opiate receptors in the central nervous system (Snyder, 1977) is likely to be the most significant contribution to the science and art of pain relief in our time. Although the search for non-addictive substances with analgesic properties comparable to those of morphine has brought as much disappointment as success, there is, at least, a clearer idea of the objectives and the possibilities. The discovery of opiate receptors in the spinal cord was soon followed by the demonstration (Wang, 1978) that the subarachnoid injection of pure preparations of morphine could effect relief of some types of acute pain; this in turn was followed by reports of the similar use of other narcotic analgesics. An interesting sequel was the preliminary report from Jerusalem that comparable results could be achieved if morphine was injected to the extradural space (Behar et al., 1979), and Cousins and others (1979) showed that when pethidine was used in this manner there was very rapid transfer of some of the drug to the spinal subarachnoid fluid.

The Israeli group appears to have maintained its lead in this type of therapy and their report of an extensive experience appears on page 247 of this issue. The method is being tried widely and the experience of Drs Wolfe and Davies from Sheffield and their recommendation of fentanyl as the drug of choice appears in our correspondence section (p. 357).

The administration of narcotics to the spinal cord appears to confer substantial analgesia in the ideal case. The method has been applied in several different circumstances—the terminal pain of cancer, the relief of pain in peripheral ischaemia, in labour and in the period after operation. In this last instance advantages are claimed over extradural injection of local anaesthetics in that cutaneous sensation in the affected region is closer to normal and the occasionally troublesome consequences of autonomic blockade are avoided. Another advantage is that the deleterious effects of narcotics on the gut (also rich in opiate receptors) is likely to be minimized, thus suggesting an earlier return of spontaneous gut motility and a reduction in the risk of clinically demonstrable ileus. On the debit side, there is the risk of inadvertent ventilatory depression from excessive amounts of narcotics entering the spinal fluid and Scott and McClure (1979) have called for caution in the use of the technique until better guidance on dosage is available.

Also in this issue Drs Nunn and Slavin present a detailed *exposé* of the applied anatomy of intercostal nerve block with special reference to postoperative pain relief after abdominal surgery (p. 253). Attention to this report will undoubtedly reduce the risk of the failure and complications associated with this type of block, although the authors remind us of limitations of the method in the treatment of patients whose abdominal wound is either extensive in the longitudinal axis or is in the mid-line.

These reports are both a challenge and a help to those who seek to advance the quality of convalescence after surgery. Perhaps they will serve also to prod the consciences of the great majority of anaesthetists, surgeons and nurses who are either content with or complacent about the open-ended prescription of i.m. narcotics as the sole remedy for suffering after surgery. The armamentarium for improvement on this is considerable and varied, not least among the possibilities being the time-honoured, if insufficiently used, techniques of i.v. narcotic administration which, in all probability, also serve to reduce the effect of such drugs on the gut. It would be a pity if all these methods were to continue to be confined to the literature and to the practice of a few enlightened enthusiasts.

A. A. Spence

REFERENCES

Behar, M., Magora, F., Olshwang, D., and Davidson, J. T. (1979). Epidural morphine in treatment of pain. *Lancet*, **1**, 527.

Cousins, M. J., Mather, L. E., Glynn, C. J., Wilson, P. R., and Graham, J. R. (1979). Selective spinal analgesia. *Lancet*, **1**, 1141.

Scott, D. B., and McClure, I. (1979). Selective epidural analgesia. *Lancet*, **1**, 1410.

Snyder, S. H. (1977). Opiate receptors in the brain. *N. Engl. J. Med.*, **296**, 266.

Wang, J. K. (1978). Pain relief by intrathecally applied serotonin or morphine. *Ann. Anaesth. Franç.*, **19**, 371.

Br. J. Anaesth. (1980), **52**, 247

OBSERVATIONS ON EXTRADURAL MORPHINE ANALGESIA IN VARIOUS PAIN CONDITIONS

F. MAGORA, D. OLSHWANG, D. EIMERL, J. SHORR, R. KATZENELSON, S. COTEV AND J. T. DAVIDSON

SUMMARY

We report the extradural administration of low-dose morphine in 10 ml of 10% dextrose (2–3 mg) to 98 adult patients with various types of acute and chronic pain. Extradural morphine injections were given either via a Tuohy needle (single or repeat injection) or via an extradural catheter. Pain relief was evaluated by subjective scoring and by the subsequent need for systemic analgesics. In 56% of patients, pain relief was considered good or excellent, in 24% it was fair, and in 20%, poor. The best results were after surgery and trauma and in patients with advanced peripheral vascular disease. The analgesia of each dose of extradural morphine lasted for 8 h (mean range 4–36 h). There was no motor, sensory or sympathetic blockade and no respiratory or haemodynamic complications. Dizziness and vomiting occurred in two patients, and urinary retention for about 12 h in three.

Recent reports have indicated that effective and prolonged pain relief can be obtained in man by the injection of small doses of morphine or pethidine into either the subarachnoid (Wang, 1978; Samü et al., 1979; Wang, Nauss and Thomas, 1979) or the extradural space (Behar et al., 1979; Cousins et al., 1979). This clinical application is based on the work of Snyder (1977a, b) and Yaksh and Rudy (1977, 1978) in animals, who attributed pain relief to a selective spinal analgesia caused by the direct action of the narcotics on specific opiate receptors that are richly distributed in the posterior horn of the spinal cord. Such an action is supported by (a) the small dose needed to abolish pain in both animals (Yaksh and Rudy, 1977) and man (Behar et al., 1979; Wang, Nauss and Thomas, 1979); (b) neurological examination which failed to demonstrate sympathetic, sensory or motor loss after narcotic treatment; (c) pharmacokinetic studies which proved that, after extradural injection of pethidine in man, the drug reached the spinal cord; (d) following adequate pain relief, the blood concentration of pethidine was much less than that found after i.v. injection of commonly used doses of this drug (Cousins et al., 1979).

The majority of clinical trials with both spinal and extradural opiate analgesia have been limited to small numbers of patients, mainly suffering from intractable pain associated with malignancy (Behar et al., 1979; Cousins et al., 1979; Wang, Nauss and Thomas, 1979). The present study reports our observations on the effect of extradural morphine in 98 patients suffering from pain of various types, with special emphasis on ischaemic and low back pain, labour pain and pain after multiple trauma or surgery, or both, accompanied by respiratory dysfunction.

PATIENTS AND METHODS

Extradural morphine was administered to 98 patients (60 women and 38 men, age range 22–82 yr), suffering from severe pain of differing origin and duration (table I). Thirty patients attended the outpatient clinic and 68 were in hospital at the time of treatment.

Of the 21 patients with low back pain, three were treated during an acute attack of radiculitis superimposed on the chronic pain, and the others had continuous uniform complaints for long periods, attributable to osteoarthritic changes, previous discectomy and similar conditions.

Among the patients afflicted with cancer, nine had diffuse intractable pain because of primary invasion of inoperable carcinoma of the cervix, bladder or colon, and seven suffered localized pain from bone metastases in the ribs, lumbar vertebrae or sacrum.

Thirty patients were women in labour: 14 at term and 16 after induced abortion with intra-amniotic prostaglandins in the second trimester of gestation.

Fifteen subjects were in acute pain from multiple trauma or surgery, or both. Three of the patients with post-traumatic pain had multiple rib fractures; one had sustained anterior fractures with consequent

---

FLORELLA MAGORA, M.D.; D. OLSHWANG, M.D.; D. EIMERL, M.D.; J. SHORR,* PH.D.; R. KATZENELSON, M.D.; S. COTEV, M.D.; J. T. DAVIDSON, M.D., F.F.A.R.C.S.; Department of Anaesthesia and *Department of Neurology, Laboratory for Neuroimmunology, Hadassah University Hospital and the Hebrew University–Hadassah Medical School, Jerusalem, Israel.

0007-0912/80/030247-06 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Pain conditions treated by single or continuous extradural administration of morphine, and results of that treatment. Number of patients*

Diagnosis	Total	Extradural morphine		Total	Results		
		Single	Continuous		Good	Fair	Poor
Low back pain	21	17	4	21	11	7	3
Pain in malignancy	16			16			
primary invasion		3	6		8	1	
bone metastases		2	5		4	3	
Labour pain	30			30			
full-term			14	14		2	12
2nd trimester induced abortion			16	16	10	6	
Pain after surgery	10			10			
abdominal			6		6		
fractured neck of femur			2		2		
varicose veins			1		1		
subtalar arthrodesis			1		1		
Post-traumatic pain	5			5			
multiple rib fractures			3		3		
lower limb fractures			2		1	1	
Ischaemic pain	5			5			
peripheral vascular disease			5		4		1
Causalgia	4	4		4		1	3
Cervical spine syndrome	2	2		2		1	1
Thrombophlebitis of lower limb (after coronary artery bypass)	2	2		2	1	1	
Old vertebral fracture	1		1	1	1		
Nephrolithiasis	1		1	1	1		
Herpes (leukaemia)	1		1	1	1		
Total	98 (100%)	30 (30.6%)	68 (69.4%)	98 (100%)	55 (56.1%)	23 (23.5%)	20 (20.4%)

flail chest, severe dyspnoea and Pa_{O_2} less than 9.3 kPa while breathing oxygen by mask ($FI_{O_2} > 0.5$). Eight of the surgical patients were elderly, presenting with various degrees of chronic obstructive lung disease: three had undergone repair of a high incisional hernia, two had aorto–femoral bypass, one had undergone cholecystectomy, and two repair of a fractured neck of femur. Five patients were given general anaesthesia, an extradural catheter being introduced after operation to permit continuous administration of morphine. This route of administration was necessary because of respiratory distress which was related, at least in part, to pain after operation. The other three patients were operated on under extradural anaesthesia. As they were known to have severe pulmonary disease, the catheter was left in place for postoperative morphine administration. The two remaining surgical patients complained of severe pain after operation in spite of large doses of narcotics.

Five patients had ischaemic pain because of peripheral vascular disease; three of these had undergone lumbar sympathectomy and vascular graft procedures 1–3 yr previously. The two other patients were undergoing aorto–femoral bypass; both had ischaemic heart disease and pre-gangrene of one or both legs. Because of excruciating pain, not relieved by large doses of narcotics and sedatives even when at rest, extradural morphine was commenced on the day of admission in both patients and was reinstated after operation in one. The other patient developed pulmonary embolism; surgery had to be postponed and extradural morphine administration was continued for 8 days.

No systemic analgesia or sedation was given for at least 6 h before treatment with extradural morphine. Except for the women in labour, none of the patients fasted. The mode of treatment was explained, and informed consent was obtained in each instance. Clinical examination laid special emphasis on localization of pain and tenderness, and limitation of movement. Each dose of morphine consisted of 2–3 ml of a 0.1% morphine–HCl solution in 10% glucose (i.e. 2–3 mg of morphine–HCl). The solution, free from preservatives, was prepared under aseptic condition in our hospital pharmacy and stored in

5-ml amber, rubber-capped vials, each containing 2–5 ml. The vials were kept in a dark place and were used within 1 month of preparation. Each dose of morphine was mixed with 8 ml of normal saline. Every effort was made to perform the extradural puncture at the level closest to the sensory innervation from the pain focus, which in most patients was in the lumbar region. In the cases of rib fractures and in patients with abdominal wounds, extradural injection was at the high and low thoracic extradural space, respectively.

Thirty patients were injected with single or repeated doses of morphine via a Tuohy extradural needle. In 68 patients, the drug was administered via an indwelling extradural catheter, one or two times daily for up to 8 days. In 10 of the obstetric patients, one dose of morphine did not suffice, and a subsequent amount of 2 mg was given 10–20 min later.

Arterial pressure, heart rate, respiratory rate and the behaviour of the patients were monitored for 1 h following the morphine injection, special attention being paid to signs of central nervous system impairment. All patients were seen again at least once in the next 24 h.

In two patients, c.s.f. morphine concentration was measured repeatedly by radioimmunoassay technique during 6 h after injection of morphine 2 mg into the extradural space. The radioimmunoassay technique used antibodies for morphine which were obtained from rabbits according to the method of Spector and Parker (1970).

The intensity of pain after treatment was evaluated by the patient: *good* when there was either complete or marked pain relief obviating the need for further analgesics for at least 4 h following the administration of morphine; *fair* when pain was diminished, function was partially improved and use of systemic analgesic drugs was considerably reduced; and *poor* when there was little or no alleviation.

RESULTS

The overall results were *good* in 56.1% of patients, *fair* in 23.5% and *poor* in 20.4% (table I). The analgesic effects were noted 8–10 min following the injection of extradural morphine, became maximal at 15–20 min, and persisted for a mean duration of 8 h (range 4–36 h).

The most favourable results were obtained in the surgical group, in the patients with multiple rib fractures and in those suffering from ischaemic pain associated with advanced peripheral vascular disease. Pain after surgery was diminished not only during absolute rest but also when associated with movement. Deep breathing became considerably more comfortable and chest breathing exercises were tolerated well. Peripheral vasoconstriction decreased, skin colour improved, and repeated blood-gas examinations showed consistent, although statistically insignificant, increases in Pa_{O_2} as compared with the pre-morphine values. The extradural catheter could be removed after 2 days of morphine treatment.

In two of the patients with ischaemic pain, morphine was discontinued after 2 days, but had to be reinstated a few hours later because of severe pain, and was subsequently maintained for 8 days. This period was the longest in our series. One to two doses of morphine daily proved to be sufficient to keep the patient free of pain, and only occasionally were sedatives necessary.

The analgesic action of extradural morphine in the patients suffering from intractable pain as a result of malignancy, and in the chronic low back pain group, reflected the overall results as presented in table I. In more than half of these two groups of patients, analgesic drugs could be either withdrawn or considerably reduced, the patient's mood and motor function improved, and a better response to various forms of conventional therapy became apparent. An exception was two patients with acute low back pain, who arrived at the clinic in distress, unable to move or lie down. Extradural morphine 2 mg failed to exert any influence, but the addition of 0.5% bupivacaine 3 ml with methylprednisolone, injected to the fourth lumbar interspace 15 min later, suppressed the pain immediately.

In 10 of the 16 patients who underwent induced abortion, extradural morphine abolished labour pain 10–20 min after commencement of treatment. The pain did not recur until the abortion process had started, sometimes many hours later. In the other six women, the morphine had no appreciable effect; addition of 0.5% bupivacaine 4 ml into the extradural space, however, proved successful and complete pain relief was obtained for as long as 6–9 h.

The effect on full-term labour pain was disappointing. A second dose of morphine 2 mg, given 10 min after the initial administration, also failed to reduce the pain. Bupivacaine 0.5% 8 ml had to be added to obtain pain relief, which sometimes lasted for up to 6 h.

None of the patients in the present series showed any signs of sympathetic denervation, loss of temperature-, touch- or pinprick sensation, or motor loss;

nor were there any adverse respiratory or haemodynamic effects.

Complications were encountered in five cases: one woman with causalgia and one man with chronic low back pain complained of dizziness, and vomited intermittently for a few hours following the morphine injection. In another patient, the dura was inadvertently punctured; the extradural needle was withdrawn and reinserted at a higher interspace. This patient, and two others, developed urinary retention over the next 12 h. One of them, an elderly male suffering from benign prostatic hypertrophy and severe ischaemic heart disease, required bladder catheterization. In all three patients, bladder function returned to normal the following day.

The radioimmunoassay tests showed clearly that the opiate was present in the cerebrospinal fluid 10–20 min after extradural injection of morphine 2 mg and that it reached peak values of 28 ng ml^{-1} after about 35 min.

DISCUSSION

Opiate drugs are known to exert a direct anti-nociceptive influence on the spinal cord (Yaksh and Rudy, 1977, 1978). This is supported by the *good* pain relief obtained in 56.1% of our heterogenous group of pain patients with only small doses of extradural morphine, and with the encouraging results of our preliminary study (Behar et al., 1979) and those reported by Cousins and others (1979) with extradural pethidine.

The morphine injected into the extradural space reached the spinal cord as demonstrated by its presence in the cerebrospinal fluid in two of our patients. Similar conclusions were drawn by Cousins and others (1979) using extradural pethidine.

The degree of pain relief in the present study was similar within each group of patients with similar pain disorders, but differed widely between groups. The patients who benefitted most were those with acute, large areas of diffuse pain such as after abdominal surgery (*good* results in all 10 patients), with multiple rib fractures (*good* in four out of five patients) and in association with ischaemic pain (*good* in four out of five patients). Although evaluation of the effect is based on the patient's subjective report and no control study was attempted, it was confirmed objectively by the marked clinical improvement in breathing and an increase in Pa_{O_2} and by the auspicious change in behaviour and mood of the patients, and their willingness and ability to function within the limits of their basic disorder. Hypoventilation and failure to take periodic deep breaths because of pain after operation and chest trauma may result in decreased FRC and intrapulmonary shunting with hypoxaemia. Pain relief often restores respiratory function and corrects the hypoxaemia (Spence and Smith, 1971; Spence and Logan, 1975). The facts that extradural morphine improved respiratory function in the surgical patients with obstructive lung disease without haemodynamic disturbances and, furthermore, succeeded in augmenting ventilation in the patient with anterior flail chest, obviating the need for mechanical ventilatory assistance, make this mode of treatment highly appropriate in such patients. An important aspect of this therapeutic modality is that it obviates systemic narcotic administration in these patients and those with ischaemic pain.

The least effect was seen in acute, localized pain such as radiculitis or causalgia. It is conceivable that in these conditions pain is caused by direct local nerve irritation accompanied by abnormal reflex activity consisting of secondary muscular spasm, which does not respond to extradural morphine. In these cases, nerve blocks with local anaesthetics known to interrupt pain transmission while producing decreased motor tone and sympathetic transmission are indicated. Therefore, whenever treatment with extradural morphine was of no avail, local anaesthetic drugs were immediately administered.

In full term labour pain also the results were poor, and even an additional extradural injection of 2 mg of morphine in 10 of the women failed to abolish pain. The failure of extradural morphine to act on the motor and sympathetic fibres may explain the lack of effect on pain in childbirth.

The results obtained in the chronic pain patients suffering from cancer and those with low back pain syndrome are comparable to the figures reported when using other forms of treatment such as physical therapy, extradural block and nerve block with anaesthetic agents and steroids (Hannington-Kiff, 1971; Defalque, 1974; Breivik et al., 1976; Ferrert, 1978) and electrical stimulation (Swerdlow, 1968; Long and Hagfors, 1975; Magora et al., 1978).

It seems that, in the disease processes where pain is the sole, or major, manifestation of the pathological disorder, extradural morphine exerts considerable influences. If, on the other hand, pain is accompanied —or caused—by secondary muscular spasm (defensive muscular contraction), sympathetic hyperexcitation or vasoconstriction, or both, the effect of extradural morphine is negligible. The mode of action of extradural morphine is most probably related to the analgesic effect of the opiate, without affecting the motor or sympathetic systems.

The results presented here are based on the effects of extradural injections of morphine, administered in doses of 2 mg. Comparable results, as reported by other investigators, were achieved while using much larger doses of extradural pethidine (100 mg) (Cousins et al., 1979) or intrathecal morphine (20 mg) (Samii et al., 1979). It is reasonable that the analgesia induced by morphine is related not only to the drug's concentration in the c.s.f. *per se*, but also to a direct endogenous inhibitory effect upon the spinal cord neurons (Cannon, Liebeskind and Frenk, 1978). If this is indeed the case, it follows that minute quantities of the morphine bind to the opiate receptors, thereby triggering secretion of endorphins. In support of this assumption are the findings of Sjölund, Terenius and Eriksson (1977) who reported low endorphin concentrations in patients suffering from chronic pain and which returned towards normal by centrally applied analgesics (Cannon, Liebeskind and Frenk, 1978).

Very high doses of regionally applied narcotics may have an additional effect upon the nerve root, or even on the peripheral nerve but, except for experimental work in the axon preparation of the squid (Simon and Rosenberg, 1970), this hypothesis still belongs in the realm of the laboratory. Evidently, large regional concentrations of morphine risk systemic effects and their use is certainly unwarranted.

A most promising feature of the treatment with low-dose extradural morphine was the lack of any adverse side-effect, thus making close and continuous patient supervision unnecessary and rendering administration of morphine through an indwelling extradural catheter most suitable for home care of patients with intractable pain (Chayen, 1979, personal communication). Furthermore, as the effect of extradural morphine is prolonged (up to 36 h) and is not associated with tachyphylaxis, neither the dose nor the frequency of therapy need to be increased for long periods of time.

From the technical point of view, if opiate analgesia indeed affects the neurons early in the ascending pain pathways, the site of injection in relation to the pain dermatome is crucial, and the drug should therefore be applied at the level innervating the pain focus. On the other hand, since extradural administration of morphine is not associated with sympathetic block, extensive extradural analgesia (thoracic or cervical) may be achieved by injecting increased amounts of the drug at a site distant from the origin of pain without the danger of consequent haemodynamic disturbance. Samii and others (1979), for instance, obtained upper thoracic analgesia in their patients, without central depression after injection of morphine 20 mg to the lumbar intrathecal space. However, until more precise and detailed studies have been conducted, injection of small doses of the opiate is advocated, given as near as possible to the pain dermatome.

Although sensory or motor loss, or postural hypotension do not appear after extradural morphine, it is advisable to keep the ambulatory patient under observation for at least 1 h after treatment since dizziness and vomiting may occur. We encountered transient urinary retention in three patients, which may be explained by the fact that morphine increases the tone of the detrusor muscle and of the vesical sphincter, thus impeding micturition (Lee and Atkinson, 1973).

As with other pain remedies, the current treatment with extradural morphine is but a battle won in the war against pain. Its beneficial features include the lack of significant side-effects as compared with other modalities utilized in pain relief and—most plausible—its setting in motion the natural defence resources of the body.

REFERENCES

Behar, M., Magora, F., Olshwang, D., and Davidson, J. T. (1979). Epidural morphine in treatment of pain. *Lancet*, **1**, 527.

Breivik, H., Hesla, P. E., Molnar, I., and Lind, B. (1976). Treatment of chronic low back pain and sciatica: comparison of caudal epidural injections of bupivacaine and methylprednisolone with bupivacaine followed by saline; in *Advances in Pain Research and Therapy*, Vol. I (eds J. J. Bonica and D. Albe-Fessard), p. 927. New York: Raven Press.

Cannon, J. T., Liebeskind, J. C., and Frenk, H. (1978). Neural and neurochemical mechanisms of pain inhibition; in *The Psychology of Pain* (ed. R. A. Steinbach), p. 27. New York: Raven Press.

Cousins, M. J., Mather, L. E., Glynn, C. J., Wilson, P. R., and Graham, J. R. (1979). Selective spinal analgesia. *Lancet*, **1**, 1141.

Defalque, R. J. (1974). Treatment of chronic pain with bupivacaine epidural blocks. *Anesth. Analg.* (*Cleve.*), **53**, 841.

Ferrert, J. B. (1978). Management of chronic dorsal root pain with epidural steroids. *Can. Anaesth. Soc. J.*, **25**, 218.

Hannington-Kiff, J. G. (1971). Treatment of intractable pain by bupivacaine nerve block. *Lancet*, **2**, 1392.

Lee, J. A., and Atkinson, R. S. (1973). *A Synopsis of Anaesthesia*, 7th edn, p. 105. Bristol: John Wright & Sons Ltd.

Long, D. M., and Hagfors, N. (1975). Electrical stimulation in the nervous system: the current status of electrical stimulation of the nervous system for relief of pain. *Pain*, **2**, 149.

Magora, F., Aladjemoff, L., Tannenbaum, J., and Magora, A. (1978). Treatment of pain by transcutaneous electrical stimulation. *Acta Anaesthesiol. Scand.*, **22**, 589.

Samii, K., Feret, J., Harari, A., and Viars, P. (1979). Selective spinal analgesia. *Lancet*, **1**, 1142.

Simon, E. J., and Rosenberg, P. (1970). Effects of narcotics on the giant axon of the squid. *J. Neurochem.*, **17**, 881.

Sjolund, B., Terenius, L., and Eriksson, M. (1977). Increased cerebrospinal fluid levels of endorphins after electro-acupuncture. *Acta Physiol. Scand.*, **100**, 382.

Snyder, S. H. (1977a). Opiate receptors and internal opiates. *Sci. Am.*, **236**, 44.

—— (1977b). Opiate receptors in the brain. *N. Engl. J. Med.*, **296**, 266.

Spector, S., and Parker, C. W. (1970). Morphine: radioimmunoassay. *Science*, **168**, 1347.

Spence, A. A., and Logan, D. A. (1975). Respiratory effects of extradural nerve block in the postoperative period. *Br. J. Anaesth.*, **47**, 281.

—— Smith, G. (1971). Postoperative analgesia and lung function: a comparison of morphine with extradural block. *Br. J. Anaesth.*, **43**, 144.

Swerdlow, M. (1968). The relief of intractable pain. Progr. in Anaesth., *Excerpta Medica Int. Congr. Ser. No.* 200, Proc. Fourth World Congr. of Anaesthesiologists, London, p. 270.

Wang, J. K. (1978). Pain relief by intrathecally applied serotonin or morphine. *Ann. Anesth. Franç.*, **19**, 371.

—— Nauss, L. A., and Thomas, J. E. (1979). Pain relief by intrathecally applied morphine in humans. *Anesthesiology*, **50**, 149.

Yaksh, T. L., and Rudy, T. A. (1977). Studies on the direct spinal action of narcotics in the production of analgesia in the rat. *J. Pharmacol. Exp. Ther.*, **202**, 411.

—— —— (1978). Narcotic analgetics. CNS sites and mechanisms of action as revealed by intracerebral injection techniques. *Pain*, **4**, 299.

OBSERVATIONS SUR L'ANALGESIE EXTRADURALE A LA MORPHINE POUR LE SOULAGEMENT DE DIVERSES DOULEURS

RESUME

Ce rapport concerne l'administration extradurale de faibles doses de morphine dans 10 ml de dextrose à 10% (2–3 mg) à 98 malades adultes souffrant de divers types de douleurs aiguës et chroniques. Les injections extradurales de morphine ont été faites soit à l'aide d'une aiguille de Tuohy (une seule injection ou injection répétée), soit à l'aide d'un cathéter extradural. Le soulagement de la douleur a été évalué par cotation subjective et par le besoin de recevoir ultérieurement d'autres agents analgésiques systémiques. Dans 56% des cas, le soulagement de la douleur a été jugé bon ou excellent, dans 24% des cas acceptable, et dans les 20% restant, médiocres. Les meilleurs résultats obtenus sont ceux qui ont suivi les interventions chirurgicales et les traumatismes de même que ceux constatés sur les patients ayant une maladie vasculaire périphérique avancée. L'analgésie provoquée par chaque dose de morphine extradurale a duré 8 h (plage moyenne 4–36 h). Il n'y a eu aucun blocage moteur, sensitif ou sympathique ni aucune complication respiratoire ou hémodynamique. Deux malades ont souffert de vertiges et de vomissements, et trois autres ont eu une rétention d'urine pendant environ 12 h.

BEOBACHTUNGEN ÜBER EXTRADURALE MORPHIUM-ANALGESIE BEI VERSCHIEDENEN SCHMERZBEDINGUNGEN

ZUSAMMENFASSUNG

Wir berichten über die extradurale Verabreichung niedriger Morphiumdosen in 10 ml von 10%iger Dextrose (2–3 mg) an 98 erwachsene Patienten mit verschiedenartigen akuten und chronischen Schmerzen. Die Morphiuminjektionen wurden entweder mit einer Tuohy-Nadel (einzeln oder wiederholt), oder über einen extraduralen Katheter verabreicht. Die Schmerzlinderung wurde durch subjektive Bewertung und durch die anschliessende Notwendigkeit für systemische Analgesie beurteilt. Bei 56% der Patienten war die Schmerzlinderung gut oder ausgezeichnet, bei 24% mittelmässig und bei 20% schwach. Die besten Resultate kamen nach Operationen und nach einem Trauma, sowie bei Patienten mit fortgeschrittenen peripheren Gefässstörungen. Die schmerzlindernde Wirkung einer jeden extradurale Morphiumdosis dauerte 8 Stunden (mittlere Dauer 4–36 Stunden). Es gab keine motorische, sensorische oder sympatische Blockierung, und keine respiratorischen oder hämodynamischen Komplikationen. Schwindel und Erbrechen erfolgten bei 2 Patienten, und Harnanhaltung über etwa 12 Stunden bei 3 Patienten.

OBSERVACIONES SOBRE ANALGESIA POR MORFINA EXTRADURAL EN VARIAS CONDICIONES DOLOROSAS

SUMARIO

Informamos sobre la administración extradural de bajas dosis de morfina en 10 ml de dextrosa al 10% (2–3 mg) a 98 pacientes adultos que padecían de distintos tipos de dolores crónicos y agudos. Se practicó la inyección de morfina extradural ya sea mediante una aguja Tuohy (inyección única o inyecciones repetidas) ya sea mediante una sonda extradural. Se hizo una evaluación del alivio del dolor por marcación subjetiva y necesidad consecuente de analgésicos sistémicos. En un 56% de los pacientes, el alivio del dolor se consideró como bueno o excelente, en un 24% fue regular y en un 20% malo. Los mejores resultados se obtuvieron después de cirujía y trauma y en pacientes con enfermedad vascular periférica avanzada. La analgesia de cada dosis de morfina extradural duró durante 8 h (duración media 4–36 h). No hubo bloqueo motor, sensorial o simpático ni tampoco complicaciones respiratorias o hemodinámicas. Dos pacientes sufrieron vómitos y vértigos y tres más tuvieron una retención orinaria durante 12 h aproximadamente.

Br. J. Anaesth. (1980), **52**, 253

POSTERIOR INTERCOSTAL NERVE BLOCK FOR PAIN RELIEF AFTER CHOLECYSTECTOMY

Anatomical basis and efficacy

J. F. Nunn and G. Slavin

SUMMARY

The human intercostal space has been studied by excision of the posterior part of the rib cage at autopsy, followed by fixation, decalcification, section and staining. Injection of India ink was used to simulate local anaesthetic. At a point 7 cm from the midline, the distance from the posterior aspect of the rib to the pleura averaged 8 mm. The intercostal nerve usually comprises a number of small bundles without any enclosing fascial sheath. The bundles lie in a triangular space bounded by the rib, the posterior intercostal membrane and the intercostalis intima muscle. The first two appear impervious to the spread of an injected solution, but the last permits spread of the injection round the internal aspect of the rib to gain access to the intercostal spaces above and below that into which the injection has been made. An injection of 3 ml will also spread medially to enter the paravertebral space and surround the sympathetic chain. A small clinical study gave excellent analgesia after operation for a mean duration of 12.3 h following unilateral intercostal block with 3 ml of bupivacaine 0.5% (with adrenaline) into each of the intercostal spaces T5–11, before cholecystectomy through a subcostal incision. There were no complications in the series.

Cholecystectomy produces one of the greatest frequencies of pain after operation and the eloquent testimony of Bevan (1964) indicates the severity which may be experienced. Pain after cholecystectomy is usually controlled by opiates, though less often by extradural analgesia (Spence and Smith, 1971). The former is less than ideal, mainly because of the intermittent character of the relief afforded by administration "as required". There may also be a reluctance on the part of the patient to request an analgesic or on the part of the staff to administer it. Extradural analgesia usually gives excellent results, but there are administrative problems in arranging for the repeat administrations to be given by someone trained to handle the complication of total spinal anaesthesia should it arise.

The present study has explored the use of unilateral posterior intercostal nerve block by the technique described by Moore (1965, 1975), not as a substitute for general anaesthesia but for control of pain after operation. Since we were unable to find an account of the detailed anatomy of the human intercostal space relevant to the technique, we undertook a study in cadavers, including spread within the intercostal space of injected India ink to simulate a local anaesthetic. In a small clinical study, we have considered the influence of the type of incision, the success rate, the duration of relief from a single injection of bupivacaine and the practical feasibility of a technique which might find widespread application.

METHODS

Anatomical study of the human intercostal space

The bony rib cage was removed in six subjects at autopsy from the posterior mid-line to the anterior axillary line and from the 2nd to the 10th rib on the left side. The rib cage was fixed in formalin and subsequently decalcified in formic acid. Blocks were taken from the following sites and sections cut so that the ribs and intercostal spaces were seen in cross-section as follows:

Posteriorly 7 cm from the mid-line:
intercostal spaces 3/4, 6/7, 9/10

In the anterior axillary line:
intercostal spaces 3/4, 6/7, 9/10

Sections were stained with haematoxylin and eosin, or with Masson's stain and mounted on 5-cm × 5-cm slides.

In one case, before removal of the rib segments, 3 ml of India ink was injected to the 6/7 intercostal

---

J. F. Nunn, PH.D., M.D., F.F.A.R.C.S., Division of Anaesthesia, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ; G. Slavin, M.B., F.R.C.PATH., F.R.C.P.(GLAS.), Division of Histopathology, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.

0007–0912/80/030253–08 $01.00

© Macmillan Journals Ltd 1980

space, 7 cm from the midline posteriorly, with the needle tip 3 mm beyond and immediately below the lower edge of the 6th rib. In a seventh subject, India ink injections were made bilaterally as described above but in the 8/9 intercostal space, and the inside of the thorax was then photographed to show the spread of the ink. Following removal of the ribs, fixation and decalcification, a vertical cut was made through the ribs at the point of the injection. The cut edge was then photographed to show the spread of ink in the fascial planes.

Clinical study

Sixteen patients (three male) received intercostal nerve blocks after the induction of anaesthesia and before the commencement of cholecystectomy through a subcostal incision. In all cases premedication was with papaveretum 10–20 mg and hyoscine 0.2–0.4 mg. Induction of anaesthesia was with thiopentone 250–400 mg and neuromuscular block was obtained with a single injection of pancuronium 5–7 mg or fazadinium 50–75 mg. Anaesthesia was maintained with 70% nitrous oxide, supplemented with small quantities of opiates. A cuffed oro-tracheal tube was passed and the lungs were ventilated artificially using a Manley ventilator which is integral in the Northwick Park anaesthetic apparatus. Surgery was usually completed within 1 h, but in a few cases lasted up to 2 h. Neuromuscular block was antagonized with neostigmine 2.5 mg given with atropine 1.2 mg.

Intercostal block was undertaken in the left lateral position and confined to the right side. The block was carried out posteriorly 7 cm from the mid-line where the angles of the ribs are superficial and easily palpated. Seven nerves were blocked extending from T5 to T11 inclusive. The needle was "walked" down the posterior surface of the rib until it just passed the inferior edge. It was then advanced 3 mm, and 3 ml of 0.5% bupivacaine (containing 1 : 200 000 adrenaline) was injected giving a total of 21 ml (105 mg of bupivacaine).

In two additional patients, the same technique was used, but cholecystectomy was carried out through a right paramedian incision.

After operation morphine 5–10 mg i.m. was prescribed for all patients "as required" and was freely available on demand.

Results were compared with a control series of 14 patients (two male) undergoing cholecystectomy by the same two surgeons using the subcostal incision and the same anaesthetic techniques.

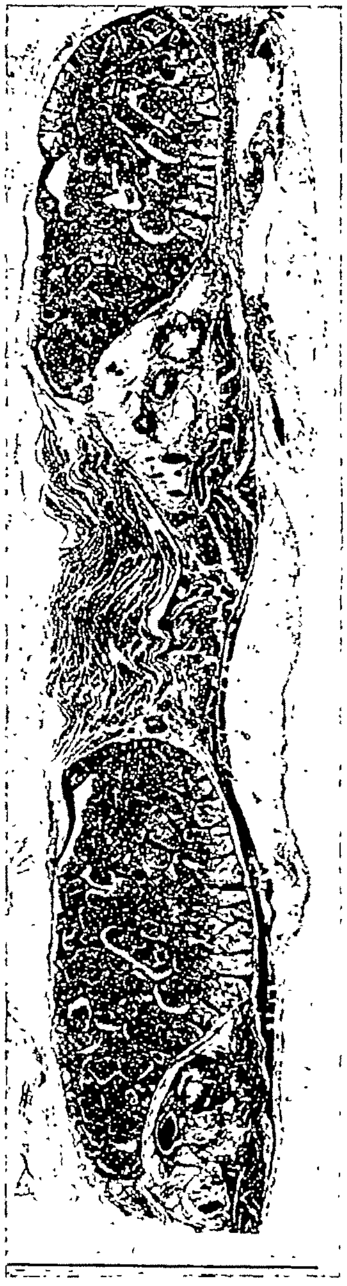


FIG. 1. Section of 6/7 intercostal space 7 cm from the midline, stained with haematoxylin and eosin and showing India ink injected to the same space. Note spread of ink between pleura and ribs but lack of penetration of posterior intercostal membrane. For identification of structures see no. 2534 (fig. 2). The bar represents 1 cm.

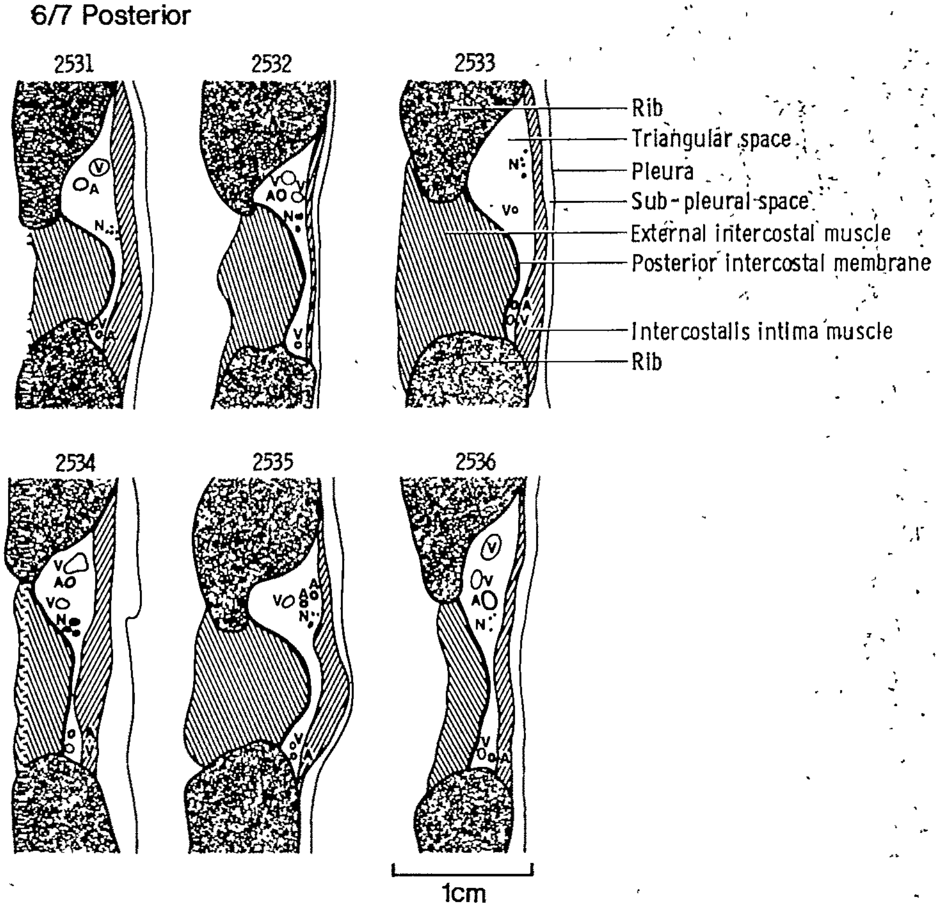


FIG. 2. Outline diagrams of 6/7 intercostal space 7 cm from the mid-line, from six subjects, to show variability in the arrangement of nerves and vessels within the triangular space. The curvature of the intercostal muscles is an artefact as a result of shrinkage of the specimen after removal from the body.

RESULTS

The anatomical study

The structure of the sixth intercostal space 7 cm from the posterior mid-line is most relevant to the nerve block technique used in the clinical study. At this point the ribs have an average thickness of about 9 mm and form one of the boundaries of a triangular space which contains the principal intercostal nerves and vessels. The triangular space (figs 1 and 2) is bounded by the inferior notched aspect of the rib (subcostal groove), the posterior intercostal membrane and the intercostalis intima. The space has an area of about 0.75 cm^2 and is largely filled with fat, through which runs the main intercostal vein, artery and nerve, usually in that order, from above downwards. There is, however, considerable variation in the individual relationships and sizes (fig. 2). For example, in one subject the artery was absent and only a small vein was found. Inferiorly the space extends to the upper border of the 7th rib and smaller vessels were often found just above the rib. The nerve trunk commonly ran as three or four separate bundles with no single neural sheath.

The external intercostal muscle is a substantial structure, bounded on its internal aspect by the clearly defined posterior intercostal membrane which replaces the internal intercostal muscle in the posterior part of the intercostal space and is impermeable to India ink in the cadaver. The intercostalis intimus muscle, however, is a flimsy structure composed of separate fascicles through which injected India ink passes freely to reach the subpleural space. It is then able to pass between ribs and pleura to reach the adjacent intercostal spaces, again passing through the fibres of the intercostalis intimus to reach the triangular compartments and the included nerves within these spaces (fig. 3). The pleura is free of any firm attachment to the ribs in this location (fig. 4). Figures 4 and 5 illustrate the very wide spread of injected India ink in the chest wall.

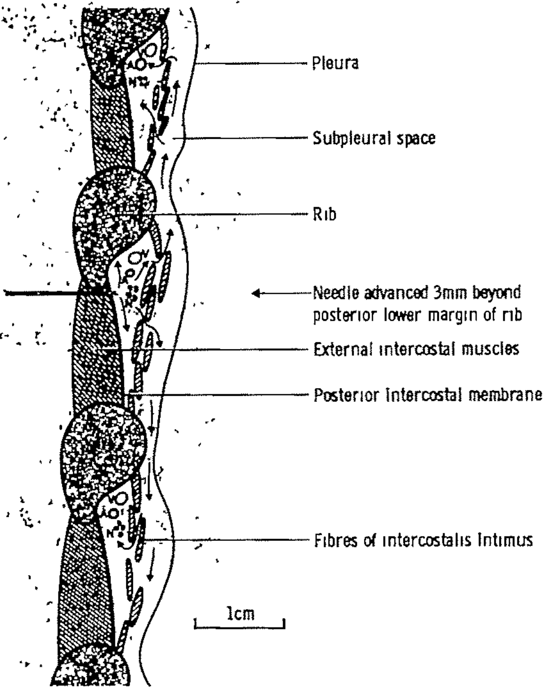

Pleura
Subpleural space
Rib
Needle advanced 3mm beyond posterior lower margin of rib
External intercostal muscles
Posterior intercostal membrane
Fibres of intercostalis intimus
1cm

FIG. 3. Schematic diagram showing the pattern of spread of solution injected 3 mm beyond the lower edge of the rib. The fascial sheath on the internal aspect of the external intercostal was impermeable to India ink.

Figure 6 shows the full range of sections from one of the subjects to demonstrate the differences in the form of the intercostal space at the different levels, and between the posterior and lateral sections. The posterior injection site is close to the angle of the rib where the internal intercostal muscle is replaced by the posterior intercostal membrane. This membrane is clearly shown in the posterior but not the lateral sections at levels 6/7 and 9/10. The intercostalis intima is poorly developed in the upper intercostal spaces. It is not seen in figure 6 in the 3/4 space and was only visible at this level in one of our six subjects.

The clinical study

The mean duration of right abdominal analgesia was 12.3 h from the end of operation (SD 5.2) as reported by the patients. The end-point was usually sharply defined and all patients were pain free for at least 5 h.

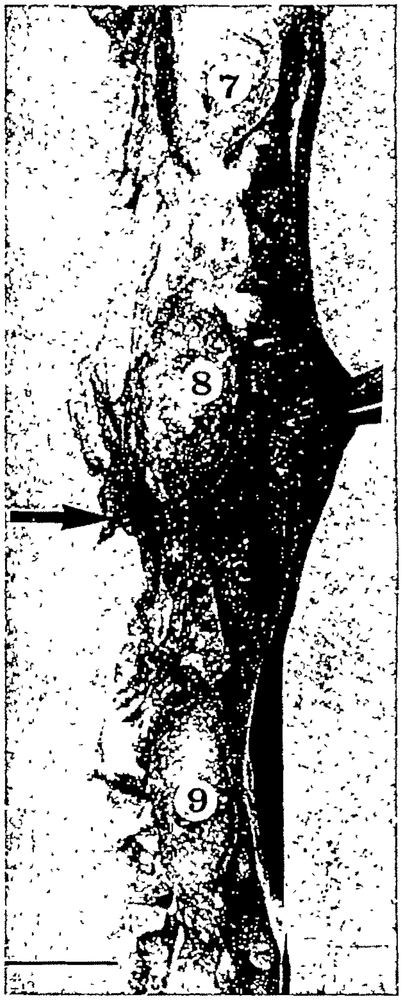


FIG. 4. Photograph of the cut ends of ribs 7, 8 and 9 to show spread of India ink (injected into 8/9 intercostal space) between the pleura and the internal surfaces of the ribs. The arrow indicates the injection site. The forceps are lifting the pleura which is quite free from attachment to the ribs. The bar represents 1 cm.

The pattern of administration of analgesics after operation is shown in figure 7. Sixty-four per cent of the control group required morphine in the first 5 h while no patient who received an intercostal block required morphine before 6 h. During the first 12 h, the control group received 1.36 injections of morphine per patient, while the corresponding figure for those with the block was only 0.44. The difference in morphine requirement continued up to 48 h (table I). The highest morphine requirement in a patient with

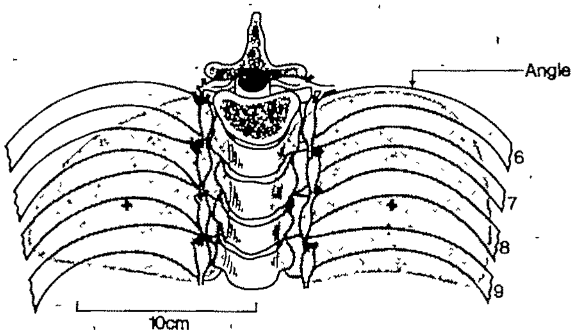


FIG. 5. The appearance of the inside of the thorax following injection of 3 ml of India ink into the 8/9 spaces at the point shown by the crosses. Note free spread of the ink into the paravertebral spaces and the adjacent intercostal spaces.

TABLE I. *Morphine requirement (mean number of injections per patient)*

	Patients receiving intercostal block	Control group
0–12 h	0.44	1.36
13–24 h	0.88	1.14
25–36 h	0.34	0.86
37–48 h	0.12	0.57
Total	1.81	3.93

intercostal block was 4 injections and, in his case, a T-tube cholangiogram showed residual stones in the common duct and there was also a klebsiella infection of the biliary tract.

All patients appeared to be completely free of pain from the area of the subcostal incision during the first few hours after operation. However, there was frequently a degree of hyperalgesia on the left side of the body. Some patients complained about discomfort from the area where a towel clip had been used on the left side. We also observed that the technique was quite unsuitable for use with a right para-median incision. There was sufficient crossing of nerve fibres in the midline for the unblocked left nerves to carry what appeared to be a quite disproportionate degree of pain.

Movement of legs and sensation in the areas of lumbar and sacral nerve distribution were normal in all patients. Five patients had normal chest radiographs with no evidence of pneumothorax. In the remaining 11 patients there was no clinical evidence of any abnormality in the chest and no radiogram was deemed necessary. No patient showed signs of chest infection after operation. One patient developed a cough, but his chest radiogram was normal. The mean time to discharge was 9 days.

DISCUSSION

Our anatomical study revealed many features of the posterior intercostal space with which, hitherto, we had been unfamiliar. First, the distance from the posterior aspect of the lower edge of the rib to the pleura averaged 8 mm, leaving a safety margin of 5 mm after advancing the tip of the needle by 3 mm. There appeared to be no occurrence of pneumothorax in this series and this we attribute to the thickness of the rib near its angle. Second, the anatomy of the intercostal nerves, although variable, is such that the recommended site of injection (fig. 3) should ensure a very high success rate. The triangular space is bounded on two sides by tissues which were impermeable to India ink and this undoubtedly helps to direct the flow of the local anaesthetic. Nevertheless, an injection incorrectly made superficial to the posterior intercostal membrane would probably result in failure. Third, we were surprised at the extent of the spread of India ink. An injection of 3 ml easily spread medially into the paravertebral space of the same intercostal space, presumably blocking the sympathetic chain (fig. 5). Since the pleura is not firmly attached to the ribs, the injection is free to pass over the internal aspect of the ribs above and below the space, with a high probability of block of the nerves in these segments (fig. 3). Fourth, the segmentation of the nerve into small bundles lying freely amongst the fat of the triangular space without any enclosing fascial sheath makes the nerve exceptionally favourable for block.

The anatomical findings accord with our clinical experience that the block was apparently successful in every case. It should also be stressed that the block is extremely simple and seven nerves can easily be blocked in 3–4 min. The posterior approach seems to have a number of advantages. The internal intercostal muscle is here replaced by the posterior intercostal membrane which probably helps to direct the injection and prevent its diffusion outwards into the external intercostal muscle. Spread of the injection cephalad and caudad is certainly free at the posterior approach, although we cannot say whether or not this is also true of the lateral approach. The medial spread to the paravertebral space is almost certainly confined to the posterior approach. We believe there may be considerable advantages in combining a sympathetic blockade with the intercostal nerve block.

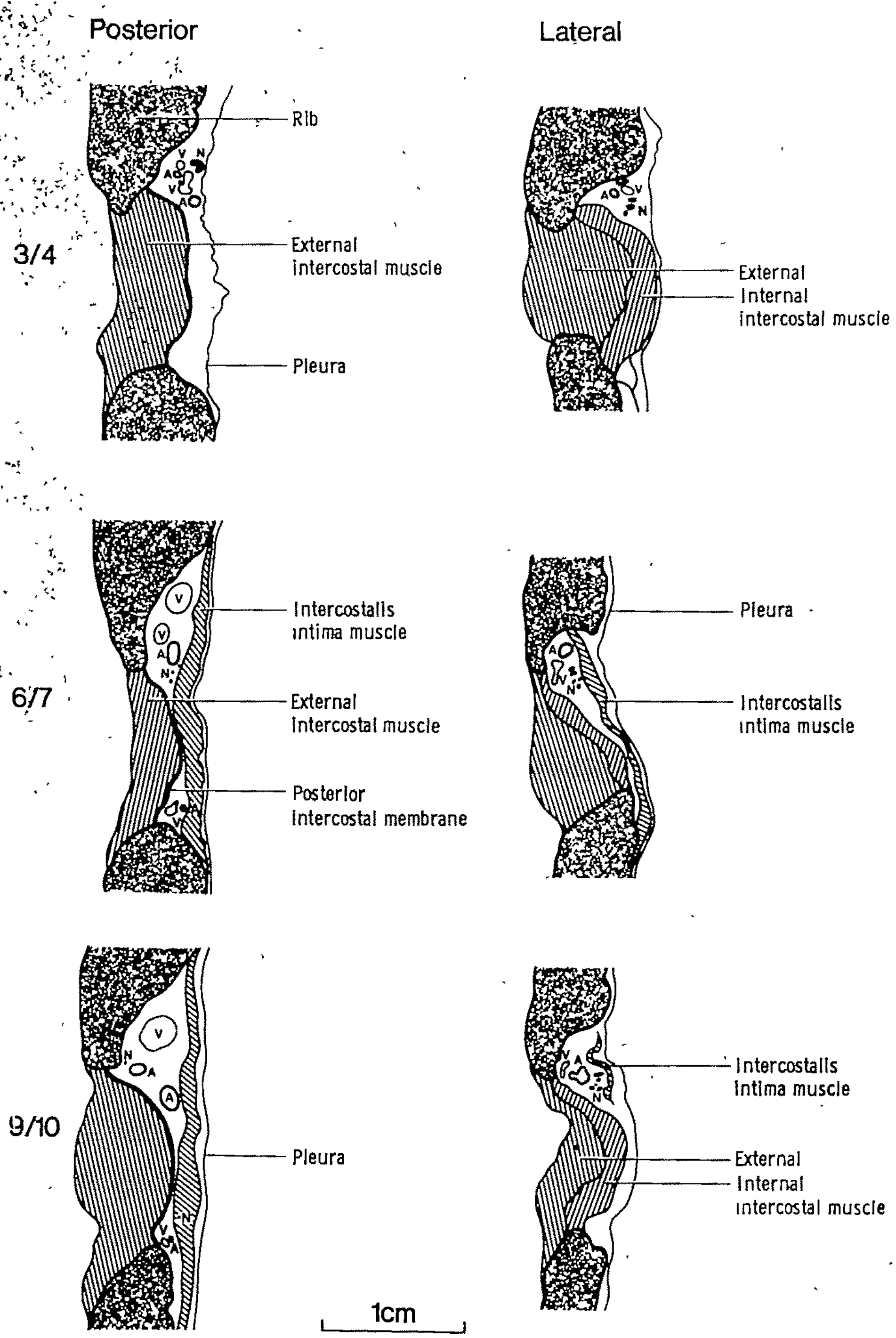


FIG. 6. Posterior and lateral sections through 3/4, 6/7 and 9/10 intercostal spaces in one subject.

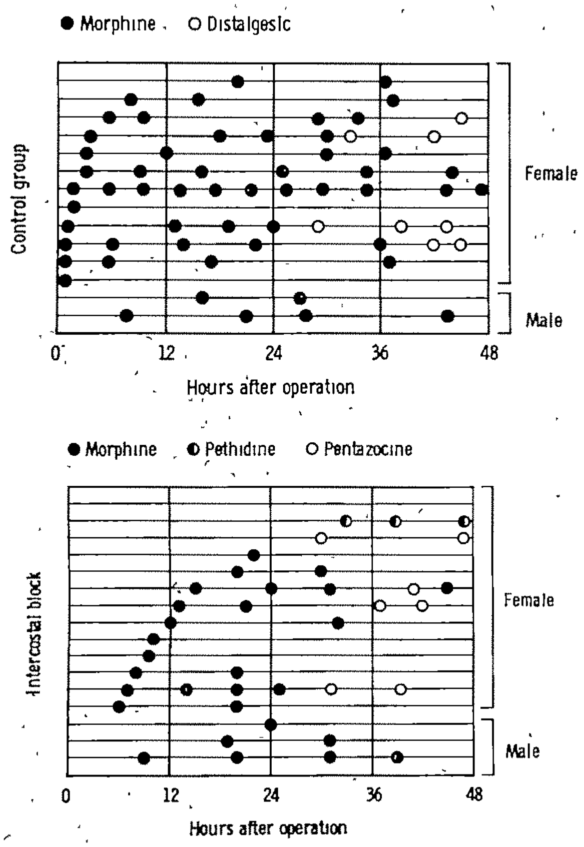


FIG. 7. Administration of analgesics after operation to a control group (upper) and to 16 patients who had right-sided intercostal block (lower).

Overall, we are convinced that right-sided lower posterior intercostal nerve block with bupivacaine is the method of choice for early control of pain after cholecystectomy through a subcostal incision. Unilateral block is unsuitable for the paramedian incision although the bilateral block would probably be suitable. The technique is much simpler than placing an extradural catheter. Intercostal block can be repeated, but none of our patients considered their pain sufficiently severe to merit this. It was, in fact, surprising that they seemed to suffer less pain during the 2nd day after operation than did the control group.

Cronin and Davies (1976) have described a series of 100 intercostal nerve blocks for relief of pain after operation, with two cases of pneumothorax. They also reviewed the literature of this complication which has a frequency of less than 1% in most series. Engberg (1975) reported a series of 76 patients who received unilateral intercostal block for postoperative pain relief after subcostal incisions. Pulmonary function was significantly better in these patients compared with a control group who received the conventional analgesic regimen.

REFERENCES

Bevan, P. G. (1964). Cholecystectomy in a surgeon. *Lancet*, 1, 214.

Cronin, K. D., and Davies, M. J. (1976). Intercostal block for postoperative pain relief. *Anaesth. Intens. Care*, **4**, 259.

Engberg, G. (1975). Single-dose intercostal nerve blocks with Etidocaine for pain relief after upper abdominal surgery. *Acta Anaesthesiol. Scand.* (Suppl.), **60**, 43.

Moore, D. C. (1965). *Regional Block. A Handbook for Use in the Clinical Practice of Medicine and Surgery*, 4th edn. Springfield: Charles C. Thomas.

—— (1975). Intercostal nerve block for postoperative somatic pain following surgery of thorax and upper abdomen. *Br. J. Anaesth.*, **47**, 284.

Spence, A. A., and Smith, G. (1971). Postoperative analgesia and lung function: a comparison of morphine with extradural block. *Br. J. Anaesth.*, **43**, 144.

BLOCAGE DU NERF INTERCOSTAL POSTERIEUR POUR LE SOULAGEMENT DE LA DOULEUR APRES UNE CHOLECYSTECTOMIE

Base anatomique et efficacité

RESUME

L'espace intercostal humain a été étudié en excisant la partie postérieure de la cage thoracique lors d'une autopsie, et en effectuant ensuite une fixation, une décalcification, une section et une coloration. On a injecté de l'encre de Chine pour simuler une anesthésie locale. A partir d'un point situé à 7 cm du milieu, la distance de l'aspect postérieur de la côte à la plèvre a été en moyenne de 8 mm. Le nerf intercostal comprend normalement un certain nombre de faisceaux sans qu'aucun d'entre eux ne soit enfermé dans une enveloppe aponévrotique. Les faisceaux sont disposés dans un espace triangulaire délimité par les côtes, la membrane intercostale postérieure et le muscle intercostal interne. Les deux premiers semblent être impénétrables à la dissémination d'une solution injectée, mais le dernier permet la dissémination de l'injection tout autour de l'aspect interne de la côte pour arriver aux espaces intercostaux se trouvant au-dessus et au-dessous de celui où l'injection a été faite. Une injection de 3 ml se disséminera aussi médialement de manière à pénétrer l'espace paravertébral et à entourer la chaîne sympathique. Une petite étude clinique a donné une excellente analgésie après l'intervention chirurgicale pendant une durée moyenne de 12,3 h, après blocage intercostal unilatéral à l'aide de 3 ml de bupivacaïne à 0,5% (avec de l'adrénaline) dans chacun des espaces intercostaux T5–11, avant la cholecystectomie par une incision sous-costale. Il n'y a eu aucune complication dans cette série.

HINTERER INTERKOSTALER NERVENBLOCKIERUNG ZWECKS SCHMERZLINDERUNG NACH CHOLECYSTEKTOMIE

Anatomische Basis und Wirksamkeit

ZUSAMMENFASSUNG

Der menschliche Interkostalraum wurde studiert, indem der hintere Teil des Brustkorbs bei einer Autopsie entfernt wurde, gefolgt von Fixierung, Entkalzifizierung, Sektion und Farbung. Indiatinte wurde eingespritzt, um ein lokales Narkosemittel zu simulieren. An einem bestimmten Punkt 7 cm von der Mittellinie war die Entfernung vom hinteren Aspekt der Rippe zum Pleura durchschnittlich 8 mm. Der Interkostalnerv besteht gewöhnlich aus einer Anzahl kleiner Bundel ohne Faszienhulle. Diese Bündel liegen in einem dreieckigen Raum begrenzt von der Rippe, der hinteren Interkostalmembrane und dem Intercostalis intima-Muskel. Die ersten beiden scheinen undurchdringlich fur die Ausbreitung einer eingespritzten Flussigkeit, der Muskel aber gestattet die Ausbreitung der Injektionsflüssigkeit rund um den internen Aspekt der Rippe, so dass die Flussigkeit zu den Interkostalräumen uber und unter demjenigen eindringen kann, in den die Injektion gemacht wurde. Eine Injektion von 3 ml verbreitet sich auch medial in den Paravertebralraum und rund um die die sympathische Kette. Eine kleine klinische Studie ergab ausgezeichnete postoperative Schmerzlinderung auf eine mittlere Dauer von 12,3 Stunden nach einer unilateralen Interkostalblockierung mit 3 ml Bupivacain 5% (mit Adrenalin) in jeden der Interkostalräume T5–11, vor Cholecystektomie durch einen subkostalen Einschnitt. In der Serie gab es keine Komplikationen.

BLOQUEO DEL NERVIO INTERCOSTAL POSTERIOR PARA EL ALIVIO DEL DOLOR DESPUES DE UNA COLECISTECTOMIA

Base anatómica y eficacia

SUMARIO

Se llevó a cabo un estudio del espacio intercostal en el humano por excisión de la parte posterior de la caja torácica durante una autopsia, seguida por la fijación, la descalcificación, la sección y la coloración. Se inyectó tinta de India para simular al anestesia local. En el punto situado a 7 cm de la línea media, la distancia del aspecto posterior de la costilla hasta la pleura alcanzaba un promedio de 8 mm. El nervio intercostal comprende habitualmente una serie de pequeños mazos sin ninguna vaina fascial de protección. Los mazos se hallan en un espacio triangular limitado por la costilla, la membrana intercostal posterior y el músculo intercostalis intima. Los dos primeros parecían impermeables a la penetración de una solución inyectada, pero el último dejó que se extiendera la inyección alrededor del aspecto interno de la costilla para entrar en los espacios intercostales por encima y por debajo del en que se había practicado la inyección. Una inyección de 3 ml también se extenderá medialmente y entrará en el espacio paravertebral para rodear la cadena simpática. Un pequeño estudio clínico arrojó una excelente analgesia después de la operación durante un periodo medio de 12,3 h después del bloqueo intercostal unilateral con 3 ml de bupivacaina al 0,5% (con adrenalina) en cada uno de los espacios intercostales T5–11, antes de la colecistectomia a través de una incisión subcostal. No hubo complicaciones en las series.

Br. J. Anaesth. (1980), **52**, 261

CONSTRICTIVE EFFECT OF PANCURONIUM ON CAPACITANCE VESSELS

C. Lee, E. Yang and M. Lippmann

SUMMARY

The effects of pancuronium 0.08 mg kg^{-1}, metocurine 0.4 mg kg^{-1} and tubocurarine 0.4 mg kg^{-1} on vascular tone were studied in 26 patients undergoing open heart surgery during total cardiopulmonary bypass. With a fixed rate of perfusion, arterial pressure is related directly to total peripheral resistance, while the volume of blood remaining in the extracorporeal reservoir is related inversely to vascular capacity, which depends primarily on venous tone. Pancuronium increased the reservoir volume (average of 780 ± SEM 250 ml ($P < 0.01$)). We conclude that under certain circumstances pancuronium constricts capacitance vessels in man.

Changes in arterial pressure may be produced by changes in cardiac output and total peripheral resistance; cardiac output may in turn alter with changing venous tone. While numerous reports have dealt with the effects of neuromuscular blockers on the heart and the total peripheral resistance, little is known about their effects on the capacitance vessel. Accordingly, the arterial and the venous responses to pancuronium, metocurine and tubocurarine in man were studied.

METHODS

Twenty-six patients (19 males) were studied during a period of total cardiopulmonary bypass for open heart surgery. They were in the ASA classification III or IV; any with congestive heart failure, or receiving sympathomimetic or sympatholytic drugs were excluded from the study. The mean body weight was 70.6 kg (SD 13.8). The age range was 21–73 yr (mean 48 ± SD 15 yr). All patients gave informed consent to the study.

Premedication was morphine sulphate 5–10 mg or pethidine 50–100 mg, and pentobarbitone 75–100 mg both injected i.m. 1 h before anaesthesia. Following induction with thiopentone 150–350 mg, in divided doses, anaesthesia was maintained with 50% nitrous oxide in oxygen and halothane 0.25–1.0%. Pancuronium 0.1 mg kg^{-1} i.v. was used to facilitate tracheal intubation. Ventilation of the lungs was controlled manually during induction and with a mechanical ventilator thereafter. Catheters were inserted for i.v. administration of drugs and sampling of arterial blood, and systemic arterial and central venous pressures and oesophageal temperature were measured using appropriate transducers.

At the start of cardiopulmonary bypass, the patient was cooled to oesophageal temperature 33 °C. The blood flow was maintained at 2200 ml m^{-2} min^{-1}, P_{CO_2} 4–5.3 kPa, and the pH between 7.34 and 7.45. P_{O_2} was 27–67 kPa. No neuromuscular blockers were used within 30 min before cardiopulmonary bypass. Approximately 20 min after establishing total bypass either pancuronium 0.08 mg kg^{-1} ($n = 7$), metocurine 0.4 mg kg^{-1} ($n = 6$) or tubocurarine 0.4 mg kg^{-1} ($n = 7$) was injected to the bypass pump; six patients (controls) did not receive a relaxant. The mean arterial pressure of the patient and the volume of blood remaining in the reservoir of the bypass pump were noted carefully for 20 min. Changes in either were compared with Student's *t* tests for unpaired group values (with *v.* without relaxant).

RESULTS

Between the four groups there were no statistically significant differences in age, body weight or non-pulsatile arterial pressure before injection of the relaxant ($P > 0.1$). In the control group the pressure increased and the volume of blood in the extracorporeal reservoir decreased with time on cardiopulmonary bypass (fig. 1). Compared with control, pancuronium was associated with an increase in the volume of blood in the reservoir ($P < 0.01$) (fig. 1). Pancuronium increased and tubocurarine decreased arterial pressure (fig. 1, 10 min), but these small

---

Chingmuh Lee, M.D.; Elaine Yang, M.D.; Maurice Lippmann, M.D.; Department of Anesthesiology, UCLA School of Medicine, Los Angeles, Ca 90024, U.S.A.

Study performed at the Harbor General Hospital Campus of UCLA School of Medicine.

0007-0912/80/030261-03 $01.00

© Macmillan Journals Ltd 1980

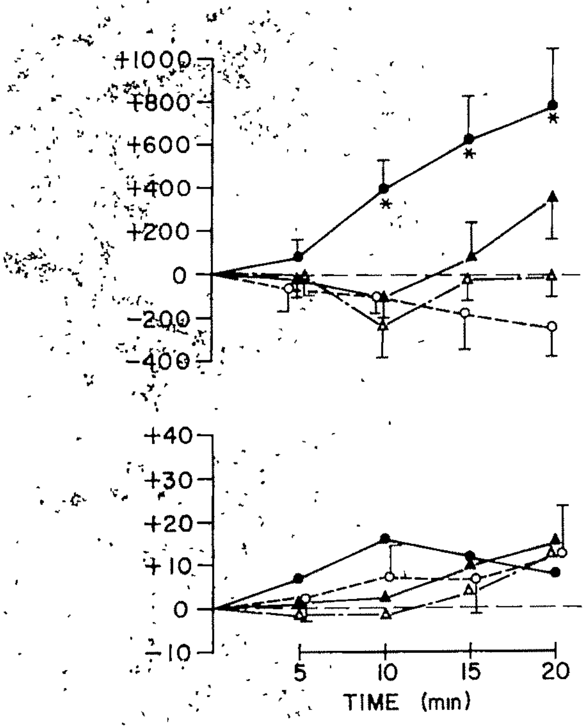


FIG. 1. Effects of pancuronium, metocurine and tubocurarine on the bypass machine reservoir volume (ml) (top) and mean arterial pressure (mm Hg) (lower). In the lower panel, most bars indicating the SEM were omitted for graphic clarity. $^*P < 0.01$. ● = pancuronium 0.08 mg kg^{-1} ($n = 7$); ▲ = metocurine 0.4 mg kg^{-1} ($n = 6$); △ = tubocurarine 0.4 mg kg^{-1} ($n = 7$); ○ = no relaxant ($n = 6$).

changes were not significantly different from control ($P > 0.1$).

DISCUSSION

With the perfusion flow rate and the central venous pressure artificially maintained constant by the bypass pump, changes in the arterial pressure are assumed to reflect changes in total peripheral resistance, which is primarily attributable to the tone of the resistance vessels. Similarly, changes in the blood volume in the pump reservoir reflect changes in the vascular capacity (the volume remaining in the patient) which is primarily determined by venous tone. Drug effects on the heart are excluded. Venous return is not a determinant of "cardiac output" in this model. Thus, we had a model in which to compare drug effects on the resistance and capacitance vessels separately. The contractility of the capacitance vessel (venous tone) is more appropriately measured as volume, rather than pressure, because the venae cavae are open to the bypass reservoir. However, the model has limitations. First, the patients are not typical of the general population. Second, there is a tendency for the arterial pressure to increase during cardiopulmonary bypass, for the volume remaining in the bypass machine to decrease, and for the volume reading to fluctuate. The gradual increase in the mean arterial pressure may be a result of reflex constriction of vessels. The volume decrease may result from transcapillary flow (Nagaoka and Katori, 1975), blood loss or vasodilatation. The fluctuating volume reading may result partially from fluctuation in the drainage of blood from the venae cavae to the bypass pump. Obviously, this model is valid only when the patient's general condition is stable and the surgical manipulation of the heart, the major vessels and the flow catheters is minimal. A control group is preferable to the use of each patient's initial data as control.

We found that pancuronium increased the blood volume remaining in the extracorporeal reservoir. Since we do not think that pancuronium can reverse the transcapillary flow, we assume that the drug has a venoconstrictive effect. Longnecker, Stoelting and Morrow (1970) observed in a similar setting that tubocurarine dilated the resistance vessel, but they did not study metocurine or pancuronium. Our data do not reveal a statistically significant vasodilator effect of tubocurarine. Many factors in the general condition of the patients and in the anaesthetic and cardiopulmonary bypass techniques may affect the autonomic tone of each patient before study. Such differences may have resulted in our observing different aspects of the vascular effects of the neuromuscular blockers. In general, it is agreed that pancuronium stimulates, metocurine is less likely to affect, and that tubocurarine depresses the autonomic and the cardiovascular systems (Loh, 1970; Smith, Proctor and Spence, 1970; Coleman et al., 1972; McCullough et al., 1972; Stoelting, 1972; Hughes, Ingram and Payne, 1976). Prevention or reduction of the re-uptake of noradrenaline (Ivankovich et al., 1975) may be part of the mechanism by which pancuronium constricts the capacitance vessel.

REFERENCES

Coleman, A. J., Downing, J. W., Leary, W. P., Moyes, D. G., and Styles, M. (1972). The immediate cardiovascular effects of pancuronium, alcuronium and tubocurarine in man. *Anaesthesia*, **27**, 415.

Hughes, R., Ingram, G. S., and Payne, J. P. (1976). Studies on dimethyl tubocurarine in anaesthetized man. *Br. J. Anaesth.*, **48**, 969.

Ivankovich, A. D., Miletich, D. J., Albrecht, R. F., and Zahed, B. (1975). The effect of pancuronium on myocardial contraction and catecholamine metabolism. *J. Pharm. Pharmacol.*, **27**, 837.

Loh, L. (1970). The cardiovascular effects of pancuronium bromide. *Anaesthesia*, **25**, 356.

Longnecker, D. E., Stoelting, R. K., and Morrow, A. G. (1970). Cardiac and peripheral vascular effects of d-tubocurarine in man. *Anesth. Analg.* (*Cleve.*), **49**, 660.

McCullough, L. S., Stone, W. A., Delaunois, A. L., Reier, C. E., and Hamelberg, W. (1972). The effect of dimethyl tubocurarine iodide on cardiovascular parameters, postganglionic sympathetic activity, and histamine release. *Anesth. Analg.* (*Cleve.*), **51**, 554.

Nagaoka, H., and Katori, M. (1975). Inhibition of kinin formation by a kallikrein inhibitor during extracorporeal circulation in open-heart surgery. *Circulation*, **52**, 325.

Smith, G., Proctor, D. W., and Spence, A. A. (1970). A comparison of some cardiovascular effects of tubocurarine and pancuronium in dogs. *Br. J. Anaesth.*, **42**, 923.

Stoelting, R. K. (1972). The hemodynamic effects of pancuronium and d-tubocurarine in anesthetized patients. *Anesthesiology*, **36**, 612.

EFFET CONSTRICTIF DU PANCURONIUM SUR LES VAISSEAUX DE CAPACITANCE

RESUME

On a étudié les effets du pancuronium à raison de 0,08 mg kg^{-1}, de la métocurarine à raison de 0,4 mg kg^{-1} et de la tubocurarine à raison de 0,4 mg kg^{-1} sur la tonicité vasculaire de 26 malades subissant une intervention chirurgicale à coeur ouvert, pendant une dérivation cardio-pulmonaire totale. Avec un taux de perfusion fixe, la pression artérielle est reliée directement à la résistance périphérique locale totale, alors que le volume du sang restant dans le réservoir extracorporel est inversement relié à la capacité vasculaire, laquelle dépend essentiellement de la tonicité veineuse. Le pancuronium a fait augmenter le volume du réservoir (moyenne de 780 ± Erreur Type des Moyennes 250 ml ($P<0{,}01$). Nous en concluons que dans certaines circonstances le pancuronium rétrécit les vaisseaux de capacitance chez l'homme.

ZUSAMMENZIEHENDE WIRKUNG VON PANCURONIUM AUF KAPAZITANZGEFÄSSE

ZUSAMMENFASSUNG

Die Wirkungen von 0,08 mg kg^{-1} Pancuronium, 0,4 mg kg^{-1} Metocurarin und 0,4 mg kg^{-1} Tubocurarin auf den Gefässtonus wurden bei 26 Patienten studiert, an denen offene Herzoperationen mit totalem Herzlungen-Bypass durchgeführt wurden. Bei einer fixierten Perfusionsrate ist der arterielle Druck direkt auf den gesamten peripheren Widerstand abgestimmt, wahrend das ausserhalb des Körpers verbleibende Blutvolumen umgekehrt proportional zur Gefasskapazität ist, die wiederum hauptsächlich vom Venentonus abhängt. Durch Pancuronium wird dieses Blutreservoir (durchschnittlich 780 ± SEM 250 ml ($P<0{,}01$)) vergrossert. Wir schliessen daraus, dass Pancuronium unter gewissen Umständen die menschlichen Kapazitanzgefässe zusammenzieht.

EFECTOS CONSTRICTORES DEL PANCURONIO EN LOS VASOS DE CAPACITANCIA

SUMMARIO

Se estudiaron los efectos de 0,08 mg kg^{-1} del pancuronio, de 0,4 mg kg^{-1} de metocurina y de 0,4 mg kg^{-1} de tubocurarina sobre el tono vascular de 26 pacientes sometidos a cirujía de corazón abierto durante una derivación cardiopulmonar total. Con un ritmo fijo de perfusión, la presión arterial se relaciona directamente con la resistencia periférica, mientras el volumen de sangre que se encuentra en el depósito extracorporal se relaciona de manera inversa con la capacidad vascular, que depende fundamentalmente del tono venoso. El pancuronio tuvo por efecto de aumentar el volumen del depósito (promedio de 780 ± SEM 250 ml ($P<0{,}01$)). Llegamos a la conclusión que, en ciertas circunstancias, el pancuronio constriñe los vasos de capacitancia en el hombre.

Br. J. Anaesth. (1980), **52**, 265

VENTILATORY DEPRESSION OF THE NEWBORN OF WOMEN RECEIVING PETHIDINE OR PENTAZOCINE

A double-blind comparative trial

S. O. Refstad and E. Lindbæk

SUMMARY

Forty-two women at term received pethidine 100 mg and 43 received pentazocine 45 mg, both given in a double-blind randomized manner. There was no difference in analgesic effect between the groups, but twelve patients were judged to need more than one injection of pentazocine, compared with seven in the pethidine group. The Apgar scores at 1 and 5 min were significantly less in the pethidine group. Four neonates in the pethidine group and two in the pentazocine group were severely depressed and received naloxone between 5 and 15 min after birth. The remainder of the infants received naloxone 200 µg i.m. 15 min after birth. From 5 min after birth, end-expiratory carbon dioxide concentrations and from 15 min transcutaneous Po_2 were recorded. A significantly smaller end-tidal carbon dioxide concentration was measured when more than one injection of pentazocine had been given. Repeated doses of pethidine, on the other hand, resulted in a greater end-tidal carbon dioxide concentration. Vigorous ventilation was even more pronounced when naloxone was given indicating an analeptic effect when two drugs with antagonistic activity are combined. At no time was transcutaneous Po_2 less than 6.1 kPa. We conclude that both pethidine and pentazocine produce adequate pain relief during labour, but more than one injection of pethidine is associated with greater neonatal depression.

Opiate analgesia is widely used in labour in spite of its ventilatory depressant effects on the newborn (Koch and Wendel, 1968) and its adverse effect on feeding (Kron, Stein and Goddard, 1966; Dubignon and Campbell, 1969).

The effect on the newborn of pethidine, the most commonly used analgesic, has recently been evaluated more thoroughly following the introduction of the pure opiate antagonist naloxone. The depressant effect of pethidine is said to persist for 48 h (Wiener, Hogg and Rosen, 1977).

Pentazocine has been shown to be a useful drug in relieving labour pain and to influence the process of labour beneficially without affecting the fetal heart rate (Filler and Filler, 1966; Mowat and Garrey, 1970).

Clinical trails, however, have failed to reveal any difference between pethidine and pentazocine with respect to neonatal depression when used in equianalgesic doses.

In addition to the indices of respiratory depression used in earlier trials, such as Apgar score and respiratory rate, we have used end-tidal carbon dioxide concentrations and transcutaneous Po_2 as non-invasive and perhaps more sensitive indices.

The specific opiate antagonist naloxone, given when the baby had reached a steady respiratory state after birth, would perhaps further unveil the existence of drug-induced ventilatory depression.

METHOD

Healthy parturients at term who were expected to have a normal delivery and who were judged by the midwife to require an analgesic were given either pethidine 100 mg or pentazocine 45 mg i.m. in a double-blind randomized order. Half the dose was repeated after 1 h if the effect was judged unsatisfactory by the midwife. A further full dose was given after 3 h if the duration of labour was prolonged. A pain scoring system was used, asking the mother about pain relief and the midwife's impression of the effect, before and 1 h after the injection: 0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain.

Promazine 25 mg i.m. was administered to every patient before the first injection of the trial drug. Nitrous oxide 50% in oxygen or a pudendal block, or both, were permitted during the last part of stage II.

At delivery, blood samples were collected from the umbilical artery and vein, placed in ice and later analysis was carried out with an Instrumentation Lab. IL 413. From a nasal catheter in the pharynx, end-tidal carbon dioxide concentrations were measured continuously with a Beckman L.B. 2

Sverre O. Refstad, M.D.; Ellen Lindbæk, M.D.; Department of Anaesthesia, Aker Hospital, Oslo, Norway.
Correspondence to S. O. R.

0007-0912/80/030265-07 $01.00

© Macmillan Journals Ltd 1980

infra-red carbon dioxide analyser (Evans, Hogg and Rosen, 1977a, b). A continuous recording was carried out for the first 30 min starting 5 min after birth, and repeated at 1 and 2 h. Gas was sampled at a flow rate of 300 ml min^{-1}. The peak carbon dioxide concentration and respiratory frequency were noted.

A transcutaneous P_{O_2} electrode (Roche 5300) was attached and recording made 15 min after birth while the neonate was breathing room air. Shortly after the initial oxygen measurement a dose of 0.2 mg of naloxone was given i.m. (Wiener, Hogg and Rosen, 1977) in order to antagonize any opiate-induced depression.

The results were evaluated by means of the Wilcoxon two-sample test with correction for ties (which is equivalent to the corresponding Mann–Whitney test).

RESULTS

Eighty-five patients were studied; 42 received pethidine and 43 received pentazocine. Twelve (27.9%) of the patients required more than one injection of pentazocine, and 7 (16.7%), more pethidine. This difference was not significant at the 5% level (table I).

TABLE I. *Distribution of the total number of doses administered*

Drug	Total no. of doses					
	1	1+½	1+½+½	1+1	1+1+½	Total
Pethidine	35	3	0	2	2	42
Pentazocine	31	8	1	3	0	43

Both groups were comparable with regard to parity, mother's weight, duration of the first stage of labour, time between injection and delivery and sex and size of the baby. Stage II of delivery was always terminated in less than 60 min according to the usual routine of the department.

TABLE II. *Number of patients with decreased* (−1), *unchanged* (0) *and improved* (+1 *or* +2) *pain score. Twenty-five patients gave birth within* 1 *h after injection and could not be evaluated* (*n.e.*)

	Improvement in pain score					
	−1	0	+1	+2	n.e.	Total
Pethidine	0	7	18	2	15	42
Pentazocine	1	10	21	1	10	43
Total	1	17	39	3	25	85

The mean improvement in pain score in the pethidine group was +0.81 compared with 0.67 in the pentazocine group (table II). The difference was not significant at the 5% level.

The policy of the department is to terminate stage II in less than 60 min. Five infants in the pethidine and four in the pentazocine group were delivered with forceps or vacuum extraction (table III). Abnormal fetal heart rate pattern during stage II was observed in three infants in both groups. Of these, two had bradycardia as a result of prolapse of the umbilical cord.

TABLE III. *Reasons for operative intervention during second stage of labour*

Complications	Pethidine	Pentazocine	Total
Slow progress (atraumatic)	5	4	9
Bradycardia	3	1	4
Deceleration (cord comp.)	0	2	2
Abnormal presentation	0	5	5
Narrow pelvis	0	1	1
	8	13	21

The umbilical arterial blood-gases at birth did not differ in the two groups (table IV).

TABLE IV. *Umbilical arterial blood-gases at birth.* P_{CO_2} *and* P_{O_2} (*kPa*); *base excess* (*mmol litre*$^{-1}$); *pH* (*units*)

Treatment	pH	P_{CO_2}	BE	P_{O_2}
Pethidine	7.25	7.07	−4.3	2.40
Pentazocine	7.25	7.02	−4.9	2.49

TABLE V. *Apgar score at* 1 *and* 5 *min*

No. of injections	Treatment	Apgar score (1 min)							
		4	5	6	7	8	9	10	Total
1	Pethidine	1	–	–	5	4	25	–	35
	Pentazocine	–	–	1	2	3	25	–	31
> 1	Pethidine	–	1	–	3	–	3	–	7
	Pentazocine	–	–	–	2	–	10	–	12
		Apgar score (5 min)							
		4	5	6	7	8	9	10	Total
1	Pethidine	–	–	1	2	1	21	10	35
	Pentazocine	–	–	–	–	1	16	14	31
>1	Pethidine	–	–	–	2	2	2	1	7
	Pentazocine	–	–	–	1	–	6	5	12

TABLE VI. *Apgar score, umbilical blood-gases (BE, mmol litre^{-1}; Po$_2$, kPa) and injection–delivery interval (I–D, min) for six patients who received naloxone between 5 and 15 min after birth*

	Apgar score		Umbilical arterial			
Drug	1 min	5 min	BE	Po$_2$	I–D	Presentation
Pethidine	4	9	−1	—	35	Normal
	7	7	−6	5.1	63	Normal
	7	6	−6	2.8	85	Normal
	9	7	0	3.1	70	Normal
Pentazocine	6	9	−5	1.9	134	Did not rotate
	7	7	−10	2.8	150	Did not rotate

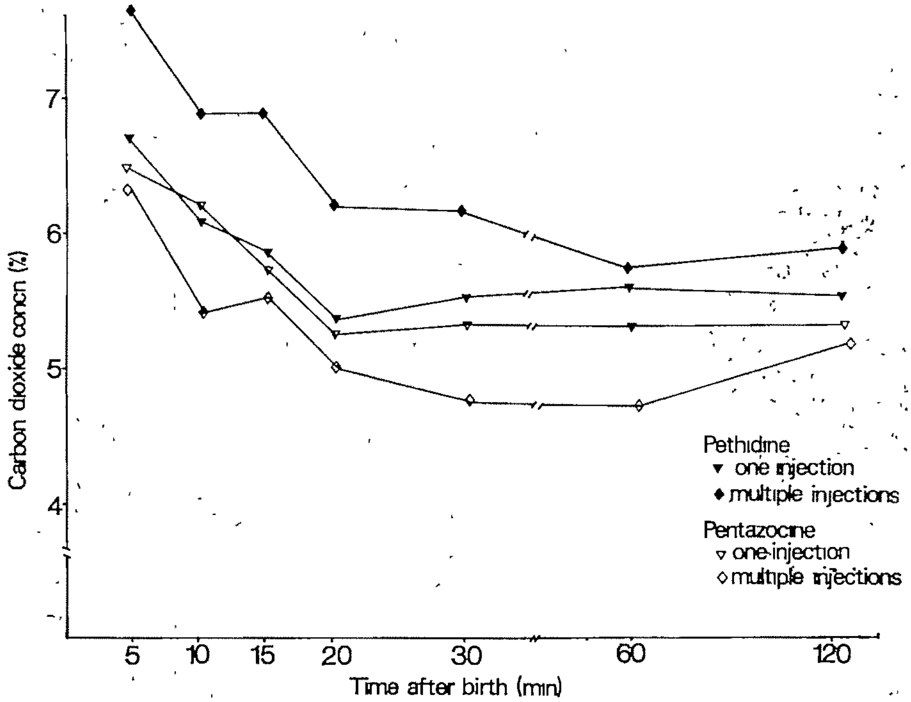


FIG. 1. End-expiratory carbon dioxide concentrations measured in the pharynx of the neonates, whose mothers had received either pethidine or pentazocine for pain relief during labour.

The Apgar scores at 1 and 5 min for the pethidine group and the pentazocine group are in table V. The Wilcoxon two-sample test showed the scores to be significantly different between the groups at 1 min ($P = 0.0329$) and at 5 min ($P = 0.0126$). The difference in total scores is accounted for by differences in respiratory effort and muscle tone and, at 5 min, in appearance.

At the time of birth six infants were judged to be severely depressed, the lungs were ventilated with oxygen, and naloxone was given between 5 and 15 min after birth. One of the mothers in the pentazocine group had received two injections, the others only one. The Apgar scores, the arterial base excess and Pco$_2$ values and the injection–delivery interval of these six neonates are in table VI. In the following results these neonates are excluded because they received the antagonist naloxone between 5 and 15 min after birth.

The median end-tidal carbon dioxide concentrations are presented in figure 1. When one injection was given there was only a slight difference between the two groups, favouring pentazocine, but not at a significant level ($P = 0.089$ at 60 min). The difference was significant when more than one injection was given to the mother ($P = 0.0014$–0.0146), with a smaller end-tidal carbon dioxide concentration for all measurement times when pentazocine was used. Comparing the values for all infants in both groups the difference was significant ($P = 0.006$–0.044) with the lower median carbon dioxide concentrations in the pentazocine group. The median end-tidal carbon dioxide concentration of the 11 neonates whose mothers had received more than one injection of pentazocine had a lower median end-tidal carbon dioxide concentration at all intervals than the neonates of patients who received only one injection. The difference was statistically significant at 30 and 60 min ($P = 0.018$ and 0.012 respectively).

After naloxone was given 15 min after birth, there was a further reduction in end-tidal carbon dioxide concentration, this being most pronounced when more than one injection of the trial drug had been given.

The percentage decrease in end-tidal carbon dioxide concentration which took place between 15 and 20 min, that is after naloxone had been given, was not significantly different in the two trial groups. This applied to the total number of neonates and also when those whose mothers received one or more than one injection were compared separately.

The frequency of ventilation in both trial groups decreased between 5 and 15 min, and then increased between 15 and 30 min followed by a slight decrease by 120 min. The mean respiratory rates at the various times of measurement are in table VII.

The overall mean values of the transcutaneous Po_2 measurements (fig. 2) show little difference between the two groups. When the results were divided according to the number of injections received, a greater effect was noticed in the pentazocine group. Those whose mothers received more than one injection of pentazocine had a lesser Po_2 than those in the pethidine groups, although not significantly so. By 2 h the two treatment groups were quite similar. No individual Po_2 value was less than 6.1 kPa, which represents more than 90% oxygen saturation in the neonate.

TABLE VII. *Mean respiratory frequency (b.p.m.) after birth*

		Time (min) after birth					
Treatment	No. of injections	5	15	20	30	60	120
Pethidine	1	44.00	41.74	42.64	46.10	44.58	43.0
Pentazocine	1	41.00	39.00	42.00	45.68	43.29	44.1
Pethidine	>1	33.14	34.00	35.14	41.14	42.14	36.7
Pentazocine	>1	41.44	34.56	45.11	48.67	44.44	42.7

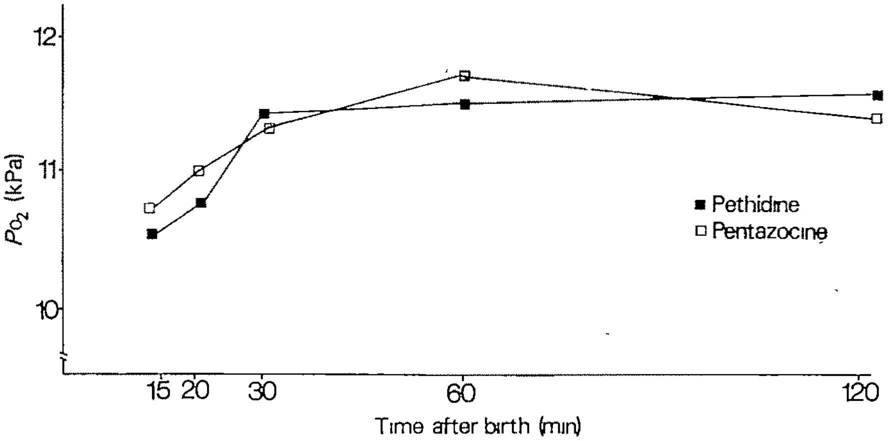


FIG. 2. Mean transcutaneous Po_2 for all neonates in both groups measured at the upper anterior part of the chest. Recordings were started 15 min after birth.

DISCUSSION

It is generally believed that the process of labour is intensified and shortened when effective analgesia is provided. Filler, Hall and Filler (1967) measured intra-uterine pressures and found an increase in the frequency and tonicity of uterine contractility when pethidine 70–100 mg or pentazocine 45 mg was given. No effect on fetal heart rate was detected. In our study there were eight obstetric complications in the pethidine group and 13 in the pentazocine group. This difference could not be attributed to a drug effect, but rather to delivery complications. This is in agreement with the results published by Borglin and Klottrup (1971) and by Duncan, Ginsburg and Morris (1969) who, incidentally, found a better Apgar score in infants whose mothers had not received an analgesic drug.

We were able to confirm observations by others that pentazocine 45 mg had approximately the same pain-relieving effect in labour as pethidine 100 mg (Odell et al., 1969; Moore, Carson and Hunter, 1970; Mowat and Garrey, 1970). However, in our study 12 of 43 patients needed more than one injection of pentazocine while seven of 42 needed more than one injection of pethidine. This may suggest that pethidine 100 mg is more potent than pentazocine 45 mg. From table I, which shows the distribution of the total doses, there is the impression that more patients were unsatisfied with the first pentazocine injection since eight parturients required an additional half dose of this drug compared with only three in the pethidine group.

The variables in the present study which indicate a depressant drug effect, such as low Apgar score, slow respiratory rate and increased end-tidal carbon dioxide concentration all seem to be in favour of pentazocine, especially when more than one injection was given. In addition, four patients in the pethidine group with normal presentation were judged to be severely depressed and were given naloxone with clinical improvement before 15 min had elapsed after birth. Two patients in the pentazocine group were also given naloxone early, but both had an abnormal presentation (table VI). Single injections of pethidine and pentazocine in our study appear to produce similar degrees of respiratory depression. Repeated doses of pentazocine did not seem to increase respiratory depression proportionally. Thus, respiratory depression following pentazocine appears to reach a maximum at a dose of approximately 60 mg per 70 kg body weight. In contrast, the respiratory depression following repeated doses of pethidine is clearly cumulative within its clinical dose range (Davie, Stephen and Scott, 1971; Dyrberg and Kolliker, 1971; Engineer and Jewnett, 1972).

Beckett found that the umbilical venous concentrations of pentazocine at the time of birth were between 40 and 70% of maternal venous concentrations, while pethidine concentrations were between 70 and 130% (Beckett and Taylor, 1967). The relative concentrations of a drug on both sides of the lipid placental membrane are dependent on a number of factors such as pKa of the drug, pH on either side of the membrane, protein binding and the rate of removal. The pH of the fetal blood is often more acid than that of maternal blood. Thus, all other factors being equal, the concentration of a basic drug will tend to be greater in fetal blood than in maternal blood (Beckett and Taylor, 1967; Moore, McNabb and Glynn, 1973).

The Apgar score is able to detect only major depressant effects. The results will vary with different observers. Additional tests, such as time for the newborn to establish sustained respiration, response to carbon dioxide rebreathing, successive blood-gas determinations, end-tidal carbon dioxide concentrations, alveolar ventilation and neuromuscular behaviour, are more objective criteria and have been used to test the effect of pethidine on neonates. To our knowledge none of these tests has been applied to test the effect of pentazocine on the newborn. Wiener, Hogg and Rosen (1977) showed that infants whose mothers received 100–300 mg of pethidine during labour, and who were given naloxone 40 μg i.v., had a smaller end-tidal carbon dioxide concentration and greater alveolar ventilation 30 min after birth than neonates receiving a placebo. This difference was not statistically significant at any other time, and no difference was observed in sucking ability, milk consumption or habituation to auditory stimulation. Using naloxone 0.2 mg i.m. within 1 min of birth, the above variables were significantly better in the naloxone-treated group than in the placebo group up to 48 h after birth.

A surprising finding in our study was that infants whose mothers received more than one injection of pentazocine had a smaller end-tidal carbon dioxide concentration than newborns whose mothers had received only one injection, assessed after naloxone had been given. Recently naloxone 0.8 mg i.v. given to adults was reported to have produced an analeptic effect (Aldrete and Goldman, 1979). Foldes and others (1963) observed no circulatory or respiratory changes in healthy adult volunteers given 5 $\mu g\ kg^{-1}$. Stephen, Cooper and Harvey (1976) found that naloxone 0.1 and 1 mg kg^{-1}, given to newborn rabbits exposed to acute anoxia, acted as a mild respiratory stimulant. Naloxone is a "pure" opiate antagonist, while pentazocine has both agonist and antagonist potentials (Kallos and Smith, 1968). The combination of two drugs with antagonist properties could in fact act additively and result in an analeptic effect. It is known that pentazocine may produce an increase in plasma catecholamines resulting in cardiovascular stimulation. This effect is different from that seen following opiates.

A major danger during labour and shortly after is hypoxia. Except for the six neonates who were judged to be severely depressed and who received oxygen and naloxone within 15 min after birth, none had a transcutaneous P_{O_2} value less than 6.1 kPa. Vigorous neonates who are crying usually produce a rapid decrease in Pa_{O_2}. We observed a decrease in transcutaneous P_{O_2} of up to 2.3 kPa. This phenomenon might explain why the less depressed children in the pentazocine group had lower oxygen tensions.

ACKNOWLEDGEMENTS

We should like to thank the Sterling-Winthrop company for supplying the trial drugs, the midwives at the obstetric department, Aker Hospital, for their helpful co-operation and Ivar Lund at Ullevål Hospital for reviewing the manuscript.

REFERENCES

Aldrete, J. A., and Goldman, E. (1979). Is naloxone a nonspecific analeptic? *Anesthesiology*, **50**, 270.

Beckett, A. H., and Taylor, J. F. (1967). Blood concentrations of pethidine and pentazocine in mother and infant at time of birth. *J. Pharm. Pharmacol.*, **19**, 50s.

Borglin, N., and Klottrup, P. (1971). Petidin och pentazocin. *Lakartidningen*, **68**, (Suppl. 3), 41.

Davie, I. T., Stephen, G. W., and Scott, D. B. (1971). The effects of premedication with pentazocine and pethidine on respiration during general anaesthesia. *Br. J. Anaesth.*, **43**, 500.

Dubignon, J., and Campbell, D. (1969). Sucking in the newborn during a feed. *J. Exp. Child Psychol.*, **7**, 282.

Duncan, S. L. B., Ginsburg, J., and Morris, N. F. (1969). Comparison of pentazocine and pethidine in normal labour. *Am. J. Obstet. Gynecol.*, **105**, 197.

Dyrberg, V., and Kolliker, K. (1971). A comparison of the effects of accumulated doses of pentazocine and pethidine on ventilation at $PA_{CO_2} = 45$ mm Hg. *Acta Anaesthesiol. Scand.*, **15**, 65.

Engineer, S., and Jennett, S. (1972). Respiratory depression following single and repeated doses of pentazocine and pethidine. *Br. J. Anaesth.*, **44**, 795.

Evans, J. M., Hogg, M. I. J., and Rosen, M. (1977a). Measurement of carbon dioxide output, alveolar carbon dioxide concentration and alveolar ventilation in the neonate. *Br. J. Anaesth.*, **49**, 453.

—— —— —— (1977b). Correlation of alveolar P_{CO_2} estimated by infra-red analysis and arterial P_{CO_2} in the human neonate and the rabbit. *Br. J. Anaesth.*, **49**, 761.

Filler, W. W., and Filler, N. W. (1966). Effect of a potent non-narcotic analgesic agent (pentazocine) on uterine contractility and fetal heart rate. *Obstet. Gynecol.*, **28**, 224.

—— Hall, W. C., and Filler, N. W. (1967). Analgesia in obstetrics. *Am. J. Obstet. Gynecol.*, **98**, 832.

Foldes, F. F., Lunn, J. N., Moore, J., and Brown, I. M. (1963). N-allylnoroxymorphone: a new potent narcotic antagonist. *Am. J. Med. Sci.*, **245**, 23.

Kallos, T., and Smith, T. G. (1968). Naloxone reversal on pentazocine-induced respiratory depression. *J.A.M.A.*, **204**, 932.

Koch, G., and Wendel, H. (1968). The effect of pethidine on the postnatal adjustment of respiration and acid base balance. *Acta Obstet. Gynaecol., Scand.*, **47**, 27.

Kron, R. E., Stein, M., and Goddard, K. E. (1966). Newborn sucking behaviour affected by obstetric sedation. *Pediatrics*, **37**, 1012.

Moore, J., Carson, R. M., and Hunter, R. J. (1970). A comparison of the effects of pentazocine and pethidine administered during labour. *J. Obstet. Gynaecol. Br. Commonw.*, **77**, 830.

—— McNabb, T. G., and Glynn, J. P. (1973). The placental transfer of pentazocine and pethidine. *Br. J. Anaesth.*, **45**, 798.

Mowat, J., and Garrey, M. M. (1970). Comparison of pentazocine and pethidine in labour. *Br. Med. J.*, **2**, 757.

Odell, E. J., Coates, B., Fox, M., Garrigan, V., Hall, M., Loye, B., Pointer, M., Trottier, Y., and Xinomilon, E. (1969). A double-blind single-dose study of pethidine and pentazocine in domiciliary obstetric practice. *Midwives Chron. Nursing Notes*, Dec. 1969, 1.

Stephen, G. W., Cooper, L. V., and Harvey, D. (1976). The effect of narcotic and narcotic-antagonist drugs in the newborn rabbit. *Br. J. Anaesth.*, **48**, 635.

Wiener, P. C., Hogg, M. I. J., and Rosen, M. (1977). Effects of naloxone on pethidine-induced neonatal depression, 1 and 2. *Br. Med. J.*, **2**, 228.

DEPRESSION VENTILATOIRE DES NOUVEAUX-NES ISSUS DE FEMMES RECEVANT DE LA PETHIDINE OU DE LA PENTAZOCINE

Etude comparative à double inconnue

RESUME

Quarante-deux femmes arrivées à terme ont reçu 100 mg de péthidine, et 43 autres ont reçu 45 mg de pentazocine, ces deux médicaments étant administrés au hasard suivant la méthode du double anonymat. Il n'y a eu aucune différence dans l'effet analgésique entre les groupes, mais il a été estimé que douze patientes avaient besoin de plus d'une seule injection de pentazocine, contre sept dans le groupe péthidine. Les indices d'Apgar à 1 min et à 5 min ont été sensiblement moindres dans le groupe péthidine. Quatre nouveaux-nés du groupe péthidine et deux du groupe pentazocine ont été sérieusement déprimés et il a fallu leur administrer du naloxone entre 5 min et 15 min

après leur naissance. On a administré aux autres bébés 200 mg de naloxone par voie intramusculaire 15 min après leur naissance. A partir de la cinquième minute qui a suivi la naissance, on a enregistré les concentrations de gaz carbonique en fin d'expiration et à partir de la quinzième minute, la $P\mathrm{o}_2$ transcutanée. On a mesuré une concentration de gaz carbonique nettement inférieure en fin de respiration lorsqu'on a administré plus d'une injection de pentazocine. Par contre, les doses répétées de péthidine ont entraîné une concentration de gaz carbonique beaucoup plus forte en fin de respiration. La ventilation vigoureuse a encore été plus prononcée lorsque le naloxone a été administré, ce qui a indiqué un effet analeptique lorsqu'on a combiné deux médicaments ayant une activité antagoniste. A aucun moment le $P\mathrm{o}_2$ transcutanée n'a été inférieure à 6,1 kPa. Nous concluons donc que la péthidine, tout comme la pentazocine, produit un soulagement adéquat de la douleur pendant le travail, mais nous avons constaté qu'une plus forte dépression des nouveaux-nés était associée à l'administration de plus d'une injection de péthidine.

VENTILATIONSUNTERDRÜCKUNG BEI NEUGEBORENEN VON MÜTTERN, DIE PETHIDIN ODER PENTAZOCIN ERHIELTEN

Ein Vergleichender Doppelblind-Versuch

ZUSAMMENFASSUNG

Zweiundvierzig gebärende Frauen erhielten 100 mg Pethidin, 43 gebärende Frauen erhielten Pentazocin 45 mg, beides auf willkürliche doppelblindweise. Die schmerzlindernde Wirkung war bei beiden Gruppen gleich, aber zwolfe Patientinnen benötigten mehr als eine Injektion von Pentazocin, verglichen mit sieben in der Pethidin-Gruppe. Die Agpar-Resultate nach 1 und 5 Minuten waren in der Pethidin-Gruppe deutlich niedriger. Vier Neugeborene in dieser und zwei in der Pentazocin-Gruppe waren schwer geschwächt und erhielten zwischen 5 und 15 Minuten nach der Geburt Naloxon. Der Rest der Kinder erhielt 200 mg Naloxon intramuskulär 15 Minuten nach der Geburt. Ab 5 Minuten nach der Geburt wurden die Endausatmungskonzentrationen von Kohlendioxyd, und ab 15 Minuten das transkutane $P\mathrm{o}_2$ registriert. Die Kohlendioxydkonzentration war wesentlich geringer, wenn mehr als eine Injektion von Pentazocin verabreicht worden war. Wiederholte Pethidin-Verabreichung hingegen fuhrte zu höheren Kohlendioxydkonzentrationen in der Endausatmung. Kräftige Belüftung war noch ausgeprägter, wenn Naloxon verabreicht wurde, was eine analeptische Wirkung anzeigt, wenn zwei Drogen mit gegenwirksamer Aktivität kombiniert werden. Zu keinem Zeitpunkt betrug das transkutane $P\mathrm{o}_2$ weniger als 6,1 kPa. Daraus schliessen wir, dass sowohl Pethidin als auch Pentazocin ausreichende Schmerzlinderung während der Wehen bieten, dass aber mehr als eine Injektion von Pethidin mit grosserer neonataler Depression verbunden ist.

DEPRESION VENTILATORIA DEL RECIEN NACIDO DE MUJERES QUE RECIBEN PETITINA O PENTAZOCINA

Una prueba comparativa doble-ciega

SUMARIO

Se administró 100 mg de petidina a 42 mujeres al termino del embarazo y 45 mg de pentazocina a 43, en ambos casos de manera casual en prueba doble-ciega. No hubo ninguna diferencia en el efecto analgésico entre los grupos, pero doce pacientes necesitaron más de una inyección de pentazocina, se estimó, en comparación con siete en el grupo de la petidina. Las marcas Agpar a 1 y a 5 min fueron significativamente menores en el grupo de la petidina. Cuatro neonatos en el grupo de la petidina y dos en el grupo de la pentazocina fueron severamente deprimidos y recibieron naloxona entre los 5 y 15 min posteriores al nacimiento. El resto de los recién nacidos recibieron 200 mg de naloxona i.m. 15 min después del nacimiento. Se llevó a cabo un registro a los 5 min después del nacimiento de las concentraciones de dióxido de carbono expiratorio terminal y a los 15 min del $P\mathrm{o}_2$ transcutáneo. Cuando se practicó más de una inyección de pentazocina, se anotó una menor concentración de dióxido de carbono respiratorio terminal. Por otro lado, repetidas dosis de petidina tuvieron como resultado una mayor concentración del dióxido de carbono respiratorio terminal. Se registró una ventilación vigorosa más acentuada al administrar naloxona, lo que indica un efecto analéptico cuando se combinan dos substancias con actividad antagonística. En ningún momento, el $P\mathrm{o}_2$ transcutáneo dse halló por debajo de 6,1 kPa. Llegamos a la conclusión que tanto la petidina como la pentazocina brindan un alivio adecuado del dolor durante el parto, pero si se administra más de una inyección de petidina, esto acarrea entonces una mayor depresión en el neonato.

Br. J. Anaesth. (1980), 52, 273

VENTILATORY MANAGEMENT OF NEONATES UNDERGOING SURGERY

A review of the first 3 years' experience in a neonatal surgical intensive care unit

A. M. MACKERSIE, D. J. HATCH AND G. M. FARNSWORTH

SUMMARY

The results of the ventilatory management of babies, obtained in the first 3 years of a neonatal surgical intensive care unit, are assessed. Overall mortality figures and detailed examination of the cause of death in individual diagnostic groups support a selective approach to intermittent positive pressure ventilation (IPPV) based mainly on clinical criteria. The adoption of a policy of prophylactic IPPV after operation would achieve virtually no improvement in mortality.

A new neonatal surgical intensive care unit was opened at the Hospital for Sick Children, London, in September 1974, with the purpose of centralizing the care of neonates undergoing non-cardiac surgery, especially with regard to ventilation. The unit is sited close to an operating theatre suite and its facilities are available to all members of the surgical staff. Respiratory care is under the joint control of the admitting surgeon and the anaesthetic department.

This paper assesses the results of the first 3 years' experience in this unit, and discusses the results in relation to the management of ventilation.

RESULTS

The numbers of patients admitted in the 1st, 2nd and 3rd years were 147, 149 and 182 respectively, a total of 478. Of these 378 had been operated on and the remaining 100 either did not require, or were considered unsuitable for, surgery. The results of meningomyelocoele surgery are shown separately (table I) and are excluded specifically from further analysis and comment.

Mortality

Table I classifies the babies in diagnostic groups, and records the numbers and mortality rates in each group. The overall mortality (excluding meningomyelocoele) was 14.1%, varying from 8.5% for abdominal surgery to 36.1% in babies with diaphragmatic hernia.

Cause of death

The primary cause of death in the 47 babies who died after surgery is shown in table II. Eighteen died as a result of additional major congenital anomalies, and all but one included a serious cardiac anomaly.

In 15 babies the primary cause of death was respiratory. Two had cystic fibrosis. The third, a baby with a mesenteric cyst, is discussed later. The remaining 12 had a diaphragmatic hernia (Bochdalek). On arrival at the Hospital for Sick Children, the average age of those babies with a diaphragmatic hernia who died was 4 h, compared with 16 h in the survivors. Only one baby with diaphragmatic hernia admitted less than 9 h after birth survived.

Five deaths were caused by septicaemia and three of these were related to i.v. feeding through a central venous cannula. Three babies died from an anastomotic leak, four from necrotizing enterocolitis and two from cerebral damage secondary to prematurity.

Intermittent positive pressure ventilation (IPPV)

Table I shows the number and percentage of patients in each diagnostic group whose lungs were ventilated artificially, together with the mortality. Of all patients 21.2% required IPPV, most frequently after operations for gastroschisis (60%) and diaphragmatic hernia (58.6%). Preoperative IPPV was required most frequently in babies with diaphragmatic hernia presenting in the first few hours of life. Artificial ventilation was often commenced before or

---

ANGELA M. MACKERSIE, B.SC., M.B., B.S., F.F.A.R.C.S.; D. J. HATCH, M.B., B.S., M.R.C.S., L.R.C.P., F.F.A.R.C.S.; GILLIAN M. FARNSWORTH,* M.B., B.CH., F.F.A.R.C.S.; Department of Anaesthesia, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

* Present address: Anaesthetic Department, St George's Hospital, Hyde Park Corner, London S.W.1.

0007-0912/80/030273-06 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Admissions to the Neonatal Surgical Unit, September 1974–September 1977*

Diagnosis	No.	Deaths	%	Ventilated	%	Ventilated and died	% of those ventilated who died
Abdominal surgery							
General	165	14	8.5	15	9.1	13	87
Exomphalos	22	2	9	2	9	2	100
Gastroschisis	15	5	33.3	9	60	5	55.5
Tracheo-oesophageal fistula/atresia	69	9	13	17	24	9	52.9
Diaphragmatic hernia	36	13	36.1	21	58.6	13	61.9
Miscellaneous	18	4	22.2	5	27.7	4	80
Total	325	47	14.5	69	21.2	46	66.7
Meningomyelocoele	53	2	3.6	1	1.8	1	100

TABLE II. *Primary cause of death (September 1974–September 1977).* † *Non-viable bowel, not ventilated*

Diagnosis	Total	Additional major congenital anomaly	Respiratory	Septicaemia	Anastomotic leak	Necrotizing enterocolitis	Cerebral
Abdominal	14	6	2	2	1†	3	0
Tracheo-oesophageal fistula	9	4	0	2	2	0	1
Diaphragmatic hernia	13	1	12	0	0	0	0
Exomphalos	2	2	0	0	0	0	0
Gastroschisis	5	1	1	1	0	1	1
Miscellaneous	4	4	0	0	0	0	0
Total	47	18	15	5	3	4	2

during transport to Great Ormond Street or immediately on arrival. Despite this active approach to the management of diaphragmatic hernia with IPPV and immediate transfer to the operating theatre, the mortality in this group remained high. Only two of the 15 babies requiring IPPV before surgery survived. However, all six babies in whom IPPV was not required before operation, survived. IPPV was required least frequently after abdominal surgery (9.1%). Only one baby died without receiving IPPV; he had undergone three resections for multiple intestinal atresia, the remaining bowel was not considered viable; ultimate survival was therefore impossible.

Duration of IPPV. Figure 1 shows that half the babies were ventilated artificially for less than 24 h. Many of these were extremely ill on admission, often with diaphragmatic hernia or abdominal disorder, and died in the 1st day of life. However, there were 10 survivors in this group: five with tracheo-oesophageal fistula, three with diaphragmatic hernia, and two with abdominal disorders. In approximately one-third of the babies the lungs were ventilated for

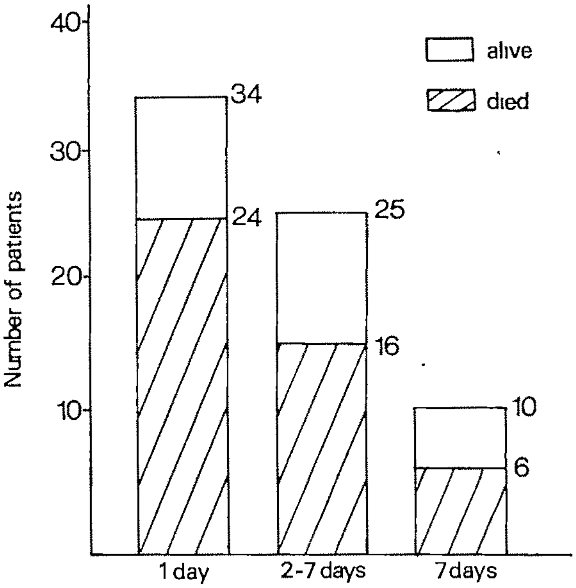


FIG. 1. Duration of ventilation.

between 1 day and 1 week, and 10 babies required ventilation for more than 1 week. The mortality in these two groups was 64% and 60% respectively. One child, with diaphragmatic hernia and tracheo-oesophageal fistula, developed bronchopulmonary dysplasia and the lungs were ventilated for 2 yr. This child has now been weaned successfully from IPPV and is alive and well.

DISCUSSION

The criteria adopted for ventilation of the lungs (IPPV) after neonatal surgery vary from centre to centre. Suutarinen (1979) advocates elective ventilation after more than 80% of operations, whilst others (Coppel et al., 1971; Inkster, 1976) recommend prophylactic IPPV for all babies in high-risk groups such as tracheo-oesophageal fistula, diaphragmatic hernia or gastroschisis. We rely on clinical assessment supported by blood-gas analysis. Increasing respiratory frequency and heart rate are clinical signs of respiratory difficulty, often accompanied by some evidence of an increase in the work of breathing, particularly flaring of the alae nasi, grunting and intercostal recession. A respiratory frequency greater than 60 b.p.m. suggests severe respiratory distress. Apnoeic attacks of short duration are not uncommon in the newborn, especially if premature. They are regarded as serious prognostic signs if they last longer than 15–20 s or cause other physiological disturbances such as bradycardia. Increases in the duration or frequency of attacks may be an indication for IPPV. The degree of spontaneous activity, including crying and ability to feed, should be recorded every 4 h and responsiveness to the measurement of arterial pressure or other simple manoeuvres noted. The state of the peripheral circulation is assessed by the quality of the peripheral pulses and temperature of the skin. Repeated clinical assessment, preferably by the same person is essential to determine whether the baby is improving or deteriorating; babies should not be allowed to become exhausted or to accumulate secretions. Any sudden deterioration should raise the possibility of pneumothorax or hypoglycaemia. The stomach is deflated with a nasogastric tube to avoid pressure on the diaphragm. A chest radiograph is always taken in babies with respiratory distress, mainly to assess the size of the heart and to exclude the rarer causes of respiratory failure such as lobar emphysema or diaphragmatic hernia. Analyses of arterial blood-gas tensions and acid–base balance provide essential support to clinical judgement, and it is helpful to know the inspired oxygen concentration during sampling. Because of the possibility of a persistent fetal circulation, arterial oxygen tension in the upper part of the body may be greater than in the lower limbs. Samples should therefore be taken from the radial artery (preferably on the right) in premature babies if retrolental fibroplasia is to be avoided. The oxygen tension of a sample taken during crying is unreliable. Although we have not laid down strict biochemical criteria for deciding when to ventilate artificially, we consider babies who are not maintaining an arterial oxygen tension between 6.7 kPa and 10.7 kPa and a carbon dioxide tension less than 6.7 kPa are likely to require ventilatory assistance. We do not hesitate, however, to commence IPPV on purely clinical grounds, even in the presence of relatively normal blood-gas tensions.

The overall mortality in the present series (14.5%) compares favourably with other published data, despite the fact that only 21% were ventilated artificially. Suutarinen (1979), ventilating 82% of cases, reports a remarkably similar overall mortality (15.4%).

However, care must be taken in any comparison of results from different centres, as so many factors are involved in mortality, including birth weight, the presence of other major congenital abnormalities, delays in diagnosis and transportation problems. In an attempt to clarify these problems we have examined the cause of death and assessed the role of IPPV in each diagnostic group.

Abdominal surgery

General. Despite the small overall mortality (8.5%), only two of the 15 babies ventilated in this group survived. However, a study of the causes of death (table III) shows that, in all but one baby, respiratory failure was secondary to other severe and progressive conditions. IPPV was used in an attempt to slow the deterioration, but could not have influenced survival, even if commenced earlier. In one baby with a mesenteric cyst our criteria for starting IPPV were not followed and cardiac arrest occurred in association with deteriorating clinical condition and blood-gas and acid–base state. In retrospect it seems possible that this child might have survived had our usual criteria been followed and IPPV started earlier.

Exomphalos. Death was caused by congenital heart disease in both of the patients who died, of the 22 in this series. These were the only two who required IPPV. The mortality (9%) compares favourably with

TABLE III. *Diagnosis and cause of death in 21 neonates after abdominal surgery (September 1974–September 1977).*
† *Not ventilated*

Diagnosis	Deaths	Cause of death
General		
Duodenal atresia	2	(1) Congenital heart disease (2) Birth wt. 1.8 kg. Candida septicaemia following i.v. feeding
Other atresias	2	(1) Renal failure. Intravascular coagulation. Septicaemia (2) Multiple atresia resected × 3. Non-viable bowel†
Meconium ileus	1	Late death. Cystic fibrosis
Hirschsprung's disease	1	Congenital heart disease
Imperforate anus	2	(1) Dysplastic kidneys (2) Congenital heart disease
Necrotizing enterocolitis	4	(1) Birth wt. 1.5 kg. Prematurity (28/52). Moribund on admission. Died during operation (2) Birth wt. 0.7 kg. Prematurity (24/52). Moribund on admission. Died during operation (3) Congenital heart disease (4) Birth wt. 1.5 kg. Gangrenous bowel. Intravascular coagulation
Others	2	(1) Ectopic bladder + congenital heart disease (2) Mesenteric cyst. Respiratory failure
Exomphalos	2	(1) Birth wt. 1.3 kg. Congenital heart disease (2) Birth wt. 2.47 kg. Congenital heart disease
Gastroschisis	5	(1) Birth wt. 1.3 kg. Intestinal obstruction after silastic closure. (Electrolyte imbalance.) Cerebral oedema (2) Birth wt. 2 kg. Gangrene of small bowel following silastic closure. Anastomotic leak following small bowel resection. Candida septicaemia following i.v. feeding (3) Birth wt. 2.5 kg. Congenital heart disease. Meconium aspiration (4) Birth wt. 1.85 kg. Cystic fibrosis. Developed disseminated intravascular coagulation, sclerema and renal failure following silastic closure (5) Birth wt. 2 kg. Developed necrotizing enterocolitis at 5 weeks after successful silastic closure

other reported series (Girven, Webster and Shandling, 1974; Rickham, Lister and Irving, 1978).

Gastroschisis. Recently introduced surgical techniques, such as the use of the silastic covering designed to reduce respiratory problems, have almost halved the mortality in this condition (Girven, Webster and Shandling, 1974). However, the mortality and the percentage ventilated artificially were greater than in those patients reported by Thomas and Atwell (1976) in whom early skin closure was used. All five deaths were again related to severe and progressive disorders where respiratory failure was an inevitable result of the baby's deteriorating condition. IPPV could not influence survival.

Tracheo–oesophageal fistula

Mortality rates for tracheo–oesophageal fistula or oesophageal atresia vary from 18% to 39% in recently published series. There were nine deaths in the present series of 69 babies, a mortality of 13%.

In 1962, Waterston, Bonham Carter and Aberdeen showed that mortality increased markedly in association with low birth weight, severity of pneumonia and presence of other major anomalies, and described three groups of patients with differing survival rates according to these factors. Group A, with the lowest mortality, comprised babies of birth weight greater than 2.5 kg who were well. Group B comprised babies weighing 1.8–2.5 kg and those of greater birth weight with moderate pneumonia or severe congenital anomaly. Group C, with highest risk, contained babies weighing less than 1.8 kg and those of greater birth weight with severe pneumonia or severe congenital anomaly. Eight of the nine babies in the present series who died had birth weights of less than 1.6 kg, and were in Waterston's highest-risk group on this criterion alone. In addition, four of these had serious congenital heart defects, which were thought to be the primary cause of death. The primary cause of death in the other four was septicaemia (two babies), anastomotic leak (one case) and massive ventricular haemorrhage with tentorial tear (one). We feel that in none of these patients was it likely that earlier commencement of IPPV would have influenced the final outcome. There was one death in a group A baby, who developed a recurrent tracheo-oesophageal fistula and pneumonia following delayed primary anastomosis at 2 months. No group B babies died during the period of this review.

Stocks (1973) suggested that respiratory difficulty may lead to disruption of the oesophageal anastomosis. Fatal anastomotic leak or recurrence of a fistula occurred in only two patients in the present series, both after delayed primary anastomosis at 2 months of age.

Diaphragmatic hernia

All the fatalities in this group of patients occurred in babies who developed respiratory distress at birth. Their mean age on arrival at hospital was 6.5 h and all received IPPV before, during and after operation until the time of death. Some required IPPV before arrival at hospital. Lung weights in these babies were small, with a mean weight of 7 g on the affected side (range 2–14 g) and 19 g on the contralateral side (range 8–30 g). Normal lung weights for individual lungs in full-term babies range from approximately 15 to 35 g (Schulz, Giordano and Schulz, 1962). Combining the weights of both lungs from these normal data in relation to body weight gives a figure of 17.2 g kg^{-1} body weight. Although some of the babies in the present series were premature, their combined lung weights were still small even when expressed in relation to body weight, with a mean value of 9.4 g kg^{-1} body weight and a range of 4.3–14.6 g kg^{-1} body weight.

Only two patients with respiratory difficulty from birth survived. Both required IPPV before operation, but not until 10 and 12 h after birth respectively. Recent experience (Collins et al., 1977; E. Sumner and J. D. Frank, in preparation) suggests that infusion of tolazoline or ligation of a patent ductus arteriosus may lead to dramatic improvement in some of these babies when they have right-to-left shunting from a persistent fetal circulation. Six babies only required IPPV after operation and all survived. The mean age at onset of respiratory symptoms in this group was 19 h and the mean age on admission was 32 h. It seems likely that these patients, and those who did not require IPPV, had less hypoplastic lungs than those whose respiratory symptoms developed earlier.

CONCLUSIONS

Examination of the causes of death in the present series, together with the overall results, supports a selective approach to IPPV based mainly on clinical criteria. It depends on careful clinical assessment and specialized care by surgical, anaesthetic, nursing and other staff. Neonatal surgery should not be undertaken in centres where this care is not available. The adoption of a policy of prophylactic postoperative IPPV in the present series would have meant that more than 70 additional babies would have been ventilated artificially each year. This policy would achieve virtually no improvement in mortality, and would require a substantial increase in staff.

ACKNOWLEDGEMENTS

We thank Sister Mary Wallace for help in collection of the data and Mr J. A. S. Dickson for advice in preparation of the manuscript. We also thank the surgeons and anaesthetists in charge of the clinical care of the patients in this series for their co-operation.

REFERENCES

Collins, D. L., Pomerance, J. J., Travis, K. W., Turner, S. W., and Papperbaum, S. J. (1977). A new approach to congenital posterolateral diaphragmatic hernia. *J. Paediatr. Surg.*, **12**, 149.

Coppel, D. L., Bennett, E. J., Ahlgren, E. W., and Stephen, C. R. (1971). The prophylactic use of a nasotracheal tube in infants under three months of age. *Surgery*, **69**, 354.

Girven, D. P., Webster, D. M., and Shandling, B. (1974). The treatment of omphalocoele and gastroschisis. *Surg. Gynaecol. Obstet.*, **139**, 222.

Inkster, J. (1976). *Recent Advances in Anaesthesia and Analgesia*, 12th edn, p. 85. London: Churchill Livingstone.

Rickham, P. P., Lister, J., and Irving, I. M. (1978). *Neonatal Surgery*, 2nd edn, p. 325. London: Butterworth.

Schulz, D. M., Giordano, D. A., and Schulz, D. H. (1962). Weight of organs of fetuses and infants. *Arch. Pathol.*, **74**, 244.

Stocks, J. G. (1973). The management of respiratory failure in infancy. *Anaesth. Intens. Care*, **1**, 486.

Suutarinen, T. (1979). Ventilatory assistance following neonatal surgery; in *Proc. Assoc. Paediatr. Anaesth.* (ed. T. R. Abbott) (in press).

Thomas, D. F. M., and Atwell, J. D. (1976). The embryology and surgical management of gastrochisis. *Br. J. Surg.*, **63**, 893.

Waterston, D. J., Bonham Carter, R. E., and Aberdeen, E. (1962). Oesophageal atresia: tracheo-oesophageal fistula: a study of survival in 218 infants. *Lancet*, **1**, 819.

TRAITEMENT VENTILATOIRE DE NOUVEAUX-NES SUBISSANT UNE INTERVENTION CHIRURGICALE

Revue de l'expérience acquise au cours des 3 premières années d'existence d'un centre de soins intensifs pour la chirurgie des nouveaux-nés

RESUME

On fait dans ce document une évaluation des résultats des traitements ventilatoires de bébés, obtenus au cours des trois premières années d'existence d'un centre de soins intensifs pour la chirurgie des nouveaux nés. Les chiffres globaux sur la mortalité et l'étude détaillée des causes de décès dans chacun des groupes de diagnostic appuient la voie d'abord sélective de la ventilation au moyen de respirateurs à pression positive intermittente (IPPV), basée surtout sur des critères cliniques. L'adoption d'une politique d'IPPV prophylactique après les interventions chirurgicales n'amènerait virtuellement aucune amélioration des chiffres de la mortalité.

BELÜFTUNGSARRANGEMENTS BEI OPERATIONEN AN NEUGEBORENEN

Ein Überblick uber die Erfahrungen der ersten drei Jahre in einer Intensivstation fur Chirurgie an Neugeborenen

ZUSAMMENFASSUNG

Die Resultate der Belüftungsvorkehrungen bei Operationen an Babies, erzielt in den ersten 3 Jahren einer chirurgischen Intensivstation für Neugeborene, werden beurteilt. Die Gesamtsterblichkeitszahlen und die genaue Untersuchung der Todesursachen in individuellen diagnostischen Gruppen befürworten eine selektive Verwendung der intermittierenden positiven Druckbelüftung (IPPV), basierend hauptsächlich auf klinischen Kriterien. Die Annahme der grundsätzlichen Methode einer prophylaktischen IPPV nach der Operation würde praktisch zu keiner Verringerung der Sterblichkeitszahlen führen.

CONTROL VENTILATORIO DE NEONATOS SOMETIDOS A CIRUJIA

Examen de la experiencia de los tres primeros años en una unidad de cuidado intensivo quirúrgico para neonatos

SUMMARIO

Se lleva a cabo una evaluación de los resultados del control ventilatorio de bebés, obtenidos durante los tres primeros años de operación de una unidad de cuidados intensivos quirúrgicos para neonatos. Las cifras de mortalidad y el examen detallado de las causas de la muerte en grupos individuales de diagnóstico apoyan un enfoque selectivo en la ventilación de presion positiva intermitente (VPPI) basada principalmente en criterios clínicos. La adopción de una política de una VPPI profiláctica después de la operación no llevaría consigo virtualmente ninguna mejoría de la mortalidad.

Br. J. Anaesth. (1980), **52**, 279

BEHAVIOUR OF UNSEDATED CHILDREN IN THE ANAESTHETIC ROOM

D. G. BEEBY AND J. O. MORGAN HUGHES

SUMMARY

The behaviour of 344 unsedated children in the anaesthetic room was assessed using a method similar to that described by Doughty (1959). The influence of the experience of the anaesthetist was found to be unimportant. The influence of the child's age was studied; children aged 7 yr and more behaved in a more satisfactory manner. The frequency of satisfactory behaviour compared favourably with that in published trials of sedative premedication which have used this method of assessment. The results support the view that the inclusion of unsedated children in such behavioural studies is essential.

Several recent trials of oral sedative premedication in children (Gordon and Turner, 1969; Boyd and Manford, 1973; Fozard and Manford, 1977; Richardson and Manford, 1979) have used methods of assessment derived from that described by Doughty (1959).

The frequency of satisfactory behaviour in the anaesthetic room of a group of children whose management did not include sedative premedication was determined. The influence of age of the child and experience of the anaesthetist were also examined. The results are compared with those obtained in published trials of sedative drugs which have employed similar methods of assessment. None of these authors included a group of unsedated children. The reader must conclude either that those authors do not agree with Doughty (1962) that such trials should have as one of their purposes an attempt to ascertain that the drugs studied "can offer any advantage over no drug at all" or that they consider the inclusion of unsedated children to be unethical.

METHODS

Children aged 2–9 yr undergoing ear, nose and throat surgery were studied. The study did not alter the usual management of such children in this hospital.

The normal practice

On the morning of the day of operation the children come to the hospital accompanied by their parents. A group of children (maximum six) are admitted together to a six-bedded unit which is used solely for this purpose. The parent stays with the child until he or she leaves the ward, just before the beginning of the afternoon operating session; the children walk with their ward nurse to a special playroom in the theatre suite. A voluntary worker reads to them, sometimes with the help of the ward nurse. Each child is given oral atropine 0.425 mg or 0.85 mg (less or more than 20 kg body weight) $1\frac{1}{2}$ h before anaesthesia. The children stay in the playroom until collected by a nurse from the paediatric theatre. The nurse walks hand-in-hand with the child to the anaesthetic room. Her sole task there is to help the child to remove his dressing gown and slippers and to settle him on the operating table. At all stages the nursing staff are encouraged to ensure that, as far as possible, the child understands what to expect.

Anaesthesia is induced with thiopentone 4–8 mg kg^{-1} i.v. followed by suxamethonium 1 mg kg^{-1}. The trachea is intubated with an oral endotracheal tube. Anaesthesia is maintained with nitrous oxide, oxygen and halothane. After operation each child is taken to the recovery area and given an analgesic drug by injection before he recovers from anaesthesia.

Assessment

Behaviour in the anaesthetic room was assessed by the anaesthetic nurse or operating department assistant using a method similar to that of Doughty (1959). Satisfactory demeanour was recorded when the child appeared sleepy, cheerful or serious. Unsatisfactory demeanour was noted when the child was apprehensive, tearful or noisy. The response to i.v. injection was recorded as satisfactory if the child showed no response or winced or whimpered.

DIANA G. BEEBY, M.B., B.S., F.F.A.R.C.S.; J. O. MORGAN HUGHES, M.B., B.CH., F.F.A.R.C.S.; Department of Anaesthetics, Norfolk and Norwich Hospital, Norwich, Norfolk.

0007-0912/80/030279-03 $01.00

© Macmillan Journals Ltd 1980

Unsatisfactory behaviour was noted if the child cried or behaved in a violent manner.

RESULTS

Three hundred and seventy-three patients were studied.

Twenty-nine questionnaires were incorrectly completed and were excluded. There were 216 children aged 7 yr or less and 128 children aged 7–9 yr.

The demeanour of 173 of 216 children in the younger age group was satisfactory compared with 108 of 128 children in the 7–9 yr age group. The difference is not statistically significant (table I).

TABLE I. *Demeanour in the anaesthetic room.* $\chi^2 = 0.71$ (n.s.)

	Age (yr)	
	Less than 7	7–9
Satisfactory	173	108
Unsatisfactory	43	20

In the younger group, the response to injection was judged satisfactory in 188 of 209 children in whom i.v. induction was attempted. In contrast, 124 of 125 children in the 7–9-yr-old group responded satisfactorily to i.v. injection. The difference is statistically significant (table II).

TABLE II. *Response to injection.* $\chi^2 = 9.345$ *(with Yates' correction) (significant at 1% level)*

	Age (yr)	
	Less than 7	7–9
Satisfactory	188	124
Unsatisfactory	21	1

Inhalation induction of anaesthesia was used in 10 children, seven of whom were aged less than 7 yr. This was at the child's request or was preferred by the anaesthetist, and this group of children was excluded from table II.

TABLE III. *Response to i.v. induction in children aged less than 7 yr. Influence of experience of the anaesthetist.* $\chi^2 = 0.076$ *(n.s.)*

	Consultant	Senior House Officer
Satisfactory	124	45
Unsatisfactory	13	4

TABLE IV. *Comparison of percentage of children with satisfactory behaviour in the present study, with results of other authors*

	Doughty (1962)		Davies and Doughty (1966)		Gordon and Turner (1969)			Boyd and Manford (1973)		Present series
	Trimeprazine	Hyoscine	Trimeprazine	Trimeprazine	Diazepam	Trimeprazine	Phenobarbitone	Diazepam	Triclofos	Atropine only
Demeanour in the anaesthetic room	71	73	79	77	88	78	70	81	88	81
Response to induction	80	94	88	79	92	72	73	91	93	94

Of the children aged 7 yr or less in whom anaesthesia was induced i.v., 137 were anaesthetized by Consultants, 49 by Senior House Officers and 23 by intermediate grades. There was no significant difference between Consultants and Senior House Officers in the frequency of unsatisfactory response to injection (table III).

DISCUSSION

The purpose of this investigation was the evaluation of the preoperative preparation for ear, nose and throat surgery of children receiving no sedative premedication. Doughty (1959) showed that the method of assessment used discriminates between the behaviour of children of less than 7 yr and those in the older age group and this was confirmed. No difference in behaviour of the children with different grades of anaesthetist was revealed.

The frequency of satisfactory behaviour of the unsedated children in this study compares favourably with that of sedated children in other studies which have employed similar methods of assessment (table IV). Different arrangements for surgery in each hospital make such comparisons difficult and an accurate description of the management of the children is essential to those whose clinical decisions may be influenced by written reports.

This study supports the view that the inclusion of unsedated children in trials of sedative premedication is both desirable and ethically justified.

ACKNOWLEDGEMENTS

We thank our surgical colleagues for permission to study their patients, the theatre staff for recording our data, Dr D. Wildon of the University of East Anglia for statistical advice and Miss B. K. Rich for typing the manuscript.

REFERENCES

Boyd, J. D., and Manford, M. L. M. (1973). Premedication in children: a controlled clinical trial of oral triclofos and diazepam. *Br. J. Anaesth.*, **45**, 501.

Davies, D. R., and Doughty, A. (1966). Oral premedication in children: the effect of varying dosage and timing. *Br. J. Anaesth.*, **38**, 878.

Doughty, A. G. (1959). The evaluation of premedication in children. *Proc. R. Soc. Med.*, **52**, 823.

—— (1962). Oral premedication in children. A controlled clinical trial of pecazine, trimeprazine and methylpentynol. *Br. J. Anaesth.*, **34**, 80.

Fozard, J. R., and Manford, M. L. M. (1977). A controlled clinical trial of oral droperidol and droperidol plus diazepam for premedication in children. *Br. J. Anaesth.*, **49**, 1147.

Gordon, N. H., and Turner, D. J. (1969). Oral paediatric premedication. A comparative trial of either phenobarbitone, trimeprazine or diazepam with hyoscine, prior to guillotine tonsillectomy. *Br. J. Anaesth.*, **41**, 136.

Richardson, F. J., and Manford, M. L. M. (1979). Comparison of flunitrazepam and diazepam for oral premedication in older children. *Br. J. Anaesth.*, **51**, 313.

COMPORTEMENT D'ENFANTS NON SOUMIS A SEDATION DANS UNE SALLE D'ANESTHESIE

RESUME

On a procédé à l'évaluation du comportement de 344 enfants non soumis à sédation dans une salle d'anesthésie, en utilisant une méthode analogue à celle décrite par Doughty (1959). On s'est rendu compte que l'influence de l'expérience de l'anesthétiste était sans importance. On a étudié l'influence de l'age de l'enfant; les enfants âgés de 7 ans et plus firent preuve d'un comportement plus approprié. La fréquence de comportement satisfaisant était comparable à celle indiquée dans les essais de prémédication sédative publiés et pour lesquels cette méthode d'évaluation a été retenue. Les résultats viennent étayer l'opinion selon laquelle il est essentiel d'inclure des enfants non soumis à sédation dans de telles études.

DAS VERHALTEN VON NICHT-SEDIERTEN KINDERN IM NARKOSERAUM

ZUSAMMENFASSUNG

Das Verhalten von 344 nicht-sedierten Kindern im Narkoseraum wurde nach einer Methode beurteilt, die ähnlich der von Doughty 1959 beschriebenen war. Der Einfluss der Erfahrung des Narkotiseurs wurde als unwichtig erfunden. Studiert wurde der Einfluss des Alters der Kinder: Kinder ab 7 Jahren verhielten sich auf befriedigendere Weise. Die Häufigkeit befriedigenden Benehmens war günstig gegenuber der bei veroffentlichten Versuchen mit sedierender Vorbehandlung, wobei ebenfalls diese Methode der Beurteilung verwendet worden war. Die Resultate verstärken die Ansicht, dass die Aufnahme nicht-sedierter Kinder in solche Verhaltensstudien essentiell ist.

COMPORTAMIENTO DE NIÑOS NO-SOMETIDOS A SEDACION EN EL CUARTO DE ANESTESIA

SUMARIO

Se llevó a cabo una evaluación del comportamiento de 344 niños no-sometidos a sedación en el cuarto de anestesia, al usar un método similar al descrito por Doughty (1959). Se comprobó que la influencia de la experiencia del anestesista importaba poco. Se estudió la influencia de la edad del niño; los niños de 7 años o más se comportaron de un modo más satisfactorio. La frecuencia de un comportamiento satisfactorio se compara favorablemente con la conducta reportada en pruebas publicadas sobre premedicación sedativa para las cuales se usó este método de evaluación. Los resultados apoyan la opinión según la cual la inclusión de niños no-sometidos a sedación es esencial en dichos estudios de comportamiento.

Br. J. Anaesth. (1980), **52**, 283

COMPARISON OF ORAL TRICLOFOS, DIAZEPAM AND FLUNITRAZEPAM AS PREMEDICANTS IN CHILDREN UNDERGOING OTOLARYNGOLOGICAL SURGERY

L. LINDGREN, L. SAARNIVAARA AND J.-J. HIMBERG

SUMMARY

Triclofos 70 mg kg^{-1}, diazepam 0.25 mg kg^{-1} and flunitrazepam 0.02 mg kg^{-1} all in combination with atropine 0.03 mg kg^{-1} were compared as oral premedicants in 128 children undergoing otolaryngological surgery in a double-blind study. All drugs provided good anxiolysis in children 5 yr and older. In children less than 5 yr, the effects of triclofos were superior to those of diazepam and flunitrazepam. There was a positive correlation between anxiolysis and the ease of induction of anaesthesia. In both age groups, flunitrazepam prevented the fasciculations caused by suxamethonium more effectively than did diazepam or triclofos. The preinduction heart rate after triclofos was greater than after the other drugs and its antisialagogue effect was superior. The mean volume of gastric contents was 0.4 ml kg^{-1} for all the patients with no statistically significant difference between the groups. The mean pH of gastric contents was 4.5 after triclofos and 2.2 after other drugs. The serum concentration of both benzodiazepines in the older age group was greater than in the younger age group.

Pethidine, diazepam or flunitrazepam given i.m. before otolaryngological surgery produce good anxiolysis in children 5 yr and older. In children less than 5 yr, the effect of pethidine and flunitrazepam was superior to that of diazepam (Lindgren, Saarnivaara and Himberg, 1979). Diazepam is absorbed better from the intestinal tract than from muscle (Assaf, Dundee and Gamble, 1975). Therefore, diazepam might be more satisfactory given orally than given i.m. In addition, oral premedicants are more acceptable to small children than painful injections.

The present study was designed to compare diazepam, flunitrazepam and triclofos as oral premedicants for children. Triclofos was included because of its satisfactory anxiolytic properties in children (Boyd and Manford, 1973). After tracheal intubation, the volume and pH of gastric content were also measured since, in paediatric anaesthesia, aspiration of gastric contents is a major hazard which would be accentuated if these were large in volume or low in pH (Salem, Wong and Collins, 1973).

PATIENTS AND METHODS

The study was carried out in 128 unselected children aged 0–15 yr. Premedication consisted of triclofos (Tricloryl syr, Glaxo, London) 70 mg kg^{-1}, diazepam (Diapam mixt, Orion, Helsinki) 0.25 mg kg^{-1} or flunitrazepam (Rohypnol gutt, Roche, Basel) 0.02 mg kg^{-1} all combined with atropine (Atropin, Orion, Helsinki) 0.03 mg kg^{-1}, given orally in 20 ml of fruit juice 96 ± 15 (SD) min before induction of anaesthesia. The children were randomly allocated to one of the three premedicant groups.

After the child's arrival in the operating room his behaviour was assessed and scored by one of the authors (L. L.) who anaesthetized all the children without knowing the premedicant. A modification of the method described by Barker and Nisbet (1973) was used for scoring the effects of premedication (table I). Children were separated into two age groups, older and less than 5 yr, and the groups were compared.

Blood samples were obtained at about 90 min and 180 min after the premedication was given in order to measure the drug concentration.

Two pictures were shown before the start of anaesthesia. Children less than 10 yr were shown and asked to identify pictures of a flower and a house and those more than 10 yr saw pictures of a shoe and a car. At 2 and 24 h after operation they were asked to recall the pictures.

L. LINDGREN, M.D.; L. SAARNIVAARA, M.D.; Otolaryngological Hospital, University of Helsinki, Haartmaninkatu 4E, SF-00290, Helsinki 29, Finland. J.-J. HIMBERG, M.D., M.SC., Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland.
Correspondence to L. L.

0007-0912/80/030283-08 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Anxiolysis score immediately before the start of anaesthesia. Total scores: 0–1.9 = poor; 2–3.9 = fair; 4–5.9 = good; 6–7 = excellent*

	Score
Behaviour of child	
Crying or struggling	0
Calm	1
Sedated	2
Drowsy	3
Sleeping but arousable	4
Reaction to venepuncture	
Crying or struggling	0
Wincing or vocalizing	1
Moving the hand	2
None	3

Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. given over 45 s. Except for children undergoing tympanotomy, the trachea was intubated following suxamethonium 1.5 mg kg^{-1} i.v. The intensity of muscle fasciculations was noted. Anaesthesia was maintained with halothane in 70% nitrous oxide in oxygen. A Rees modification of Ayre's T-piece was used for children weighing less than 25 kg and a circle system with carbon dioxide absorption for the remainder. Ventilation of the lungs was assisted or controlled. The arterial systolic pressure was measured indirectly and the heart rate was measured, using a precordial stethoscope, before and after injection of thiopentone, 30 s after intubation and every 5 min during the operation. The occurrence of any side-effects was noted.

The assessment of volume and pH of gastric contents was based on the method of Salem and others (1976). After intubation, a plastic catheter was introduced into the stomach and the contents were aspirated. Manual pressure on the upper abdomen was used to ensure gastric emptying. The position of the catheter was verified by auscultation during insufflation of a few ml of air. The volume of gastric contents per kg of body weight was calculated. The pH was estimated with a colour-indicator paper (Acilit, Merck, Darmstadt).

For comparison, the volume and pH of gastric contents were also assessed from children receiving pethidine 1 mg kg^{-1} and atropine 0.02 mg kg^{-1} i.m. 45 min before the start of anaesthesia.

At the beginning of the operation, the otolaryngologist classified the antisialagogue effect as *satisfactory* if the oropharynx was dry or moist and as *unsatisfactory* if it was wet or very wet (Boyd and Manford, 1973).

The concentrations of diazepam and flunitrazepam in serum were assessed as described in our previous paper (Lindgren, Saarnivaara and Himberg, 1979).

RESULTS

The two age groups studied were comparable in terms of sex, age, weight and haemoglobin concentration (table II).

Figure 1 shows that triclofos produced a good anxiolytic effect in the children less than 5 yr whereas the effect of diazepam was fair and that of flunitrazepam was poor. These differences were of statistical significance between both benzodiazepines and triclofos and also between the two benzodiazepines ($P<0.05$; $P<0.001$; $P<0.01$). All premedicants produced a good anxiolytic effect in the children 5 yr and older. The effect of the benzodiazepines was significantly better in the older children than in the younger ones ($P<0.01$; $P<0.001$). For com-

TABLE II. *Characteristics of premedicant groups. Mean value ± SD. Number of children in parentheses*

Premedicant group	Male	Age (yr)	Weight (kg)	Haemoglobin concn ($g\ litre^{-1}$)
Less than 5 yr				
Triclofos (21)	17	3.0 ± 1.5	15.0 ± 4.3	128.5 ± 6.1
Diazepam (18)	11	2.7 ± 1.3	12.8 ± 2.9	125.9 ± 6.0
Flunitrazepam (19)	13	2.6 ± 1.2	13.7 ± 3.2	125.8 ± 7.4
I.m. pethidine (17)	12	3.2 ± 1.3	15.0 ± 3.6	126.0 ± 9.9
5 yr and more				
Triclofos (20)	14	8.1 ± 1.4	27.7 ± 5.2	132.3 ± 5.7
Diazepam (20)	10	8.9 ± 2.7	29.8 ± 9.3	133.6 ± 6.4
Flunitrazepam (30)	17	8.9 ± 2.6	29.5 ± 7.5	133.8 ± 6.4
I.m. pethidine (13)	8	8.5 ± 2.4	30.1 ± 9.2	138.2 ± 4.6

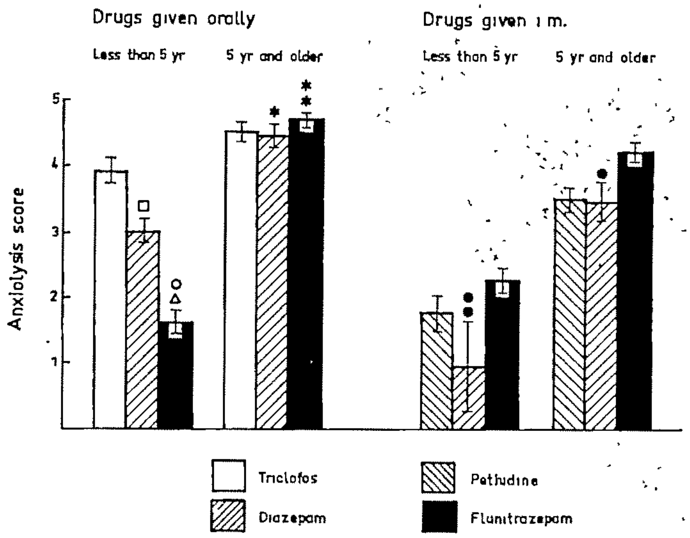


FIG. 1. Anxiolysis in different treatment groups before the start of anaesthesia. Mean values ± SEM for 18–30 children. Significant difference from triclofos in the children less than 5 yr: □ = $P<0.05$; △ = $P<0.001$. Significant difference from diazepam in the children less than 5 yr: ○ = $P<0.01$. Significant difference from the corresponding groups of children less than 5 yr: *$P<0.01$; **$P<0.001$. Significant difference from the corresponding oral groups: ● = $P<0.05$; ● ● = $P<0.01$. Results for i.m. premedicants from Lindgren, Saarnivaara and Himberg (1979).

parison, figure 1 also shows the results from our previous study (Lindgren, Saarnivaara and Himberg, 1979). The most pronounced difference between the studies was that, in both age groups, diazepam given orally produced a significantly better anxiolytic effect than when given i.m. ($P<0.05$; $P<0.01$).

Table III shows that in all premedicant groups sleep following thiopentone was more often restless (child crying or moving) in the younger (43–74%) than in the older children (5–10%). Induction was more often peaceful in the younger children premedicated with triclofos or diazepam than in those premedicated with flunitrazepam. The frequency of apnoea following thiopentone ranged from 28 to 90% in different groups. The smallest frequency occurred in the younger children premedicated with flunitrazepam and the greatest in the older children premedicated with diazepam. Eyelash reflex and eye

TABLE III. *Frequency (%) of induction characteristics using different premedicants. Number of children in parentheses. Premedicant groups different from children less than 5 yr: †$P<0.02$; ‡$P<0.01$; ¶$P<0.001$. Same age groups different from triclofos: *$P<0.05$; **$P<0.02$; and from diazepam: §$P<0.02$; §§$P<0.01$; §§§$P<0.001$. Moderate = small fine movements in face, neck, fingers and trunk; violent = vigorous movements in extremities*

Premedicant	Restless falling asleep	Frequency of apnoea (%)	Eyelash reflex present	Eye movements present	Fasciculations after suxamethonium		
					None	Moderate	Violent
Triclofos 70 mg kg^{-1}							
Less than 5 yr (21)	43	67	0	0	6	56	38
Older than 5 yr (20)	5‡	55	0	0	20	47	33
Diazepam 0.25 mg kg^{-1}							
Less than 5 yr (18)	53	75	0	0	13	20**	67
Older than 5 yr (20)	5¶	90**	0	0	6	41	53
Flunitrazepam 0.02 mg kg^{-1}							
Less than 5 yr (19)	74*	28**§§	0	0	22	64§§	14§§§
Older than 5 yr (30)	10¶	60†	3	3	8	76§	16§

TABLE IV. *Heart rate (mean ± SEM) after the child's arrival in the operating room before venepuncture and percentage of children with satisfactory or unsatisfactory antisialagogue effect classified by the otolaryngologist at the beginning of the operation. Sixteen to 30 children in the groups. Same age groups different from triclofos:* $^*P<0.05$: $^{**}P<0.02$: $^{***}P<0.01$

Premedicant group	Heart rate (beat min^{-1})	Antisialagogue effect (%) Satisfactory	Unsatisfactory
Triclofos 70 mg kg^{-1}			
Less than 5 yr	142.6 ± 5.0	100	0
Older than 5 yr	120.8 ± 3.9	95	5
Diazepam 0.25 mg kg^{-1}			
Less than 5 yr	149.7 ± 4.1	88	12
Older than 5 yr	106.5 ± 4.6*	78	22
Flunitrazepam 0.02 mg kg^{-1}			
Less than 5 yr	146.9 ± 6.9	79*	21*
Older than 5 yr	107.2 ± 4.1**	63***	37***

movements almost always disappeared in all groups. In both age groups, the fasciculations following suxamethonium were violent more often in the children premedicated with diazepam than with flunitrazepam. Neither of the benzodiazepine groups differed significantly from triclofos.

Table IV and figure 2 show the cardiovascular data. After arrival in the operating room, the heart rate in the younger children ranged from 143 to 150 beat min^{-1}. The corresponding range in the older children was 107–121 beat min^{-1}. In the older age group, the heart rate after both benzodiazepines was significantly slower than after triclofos (diazepam $P<0.05$; flunitrazepam $P<0.02$). In both benzodiazepine groups, there was one child who later needed atropine since the heart rate was less than 60 beat min^{-1}. Immediately after injection, thiopentone decreased systolic arterial pressure by 9–15 mm Hg in different groups. After tracheal intubation, the increase in systolic arterial pressure ranged from 25 to 45 mm Hg in different groups. This increase was significantly more pronounced in the older children premedicated with diazepam than in the corresponding younger age group ($P<0.01$).

Table IV also shows that a satisfactory antisialagogue effect occurred in 98, 93 and 71% of the children premedicated with triclofos, diazepam and flunitrazepam, respectively. Flunitrazepam was significantly inferior to triclofos.

As regards amnesia the difference between the groups as assessed 2 and 24 h after operation was not significant. The amnesic rate varied from 10 to 30% between the groups.

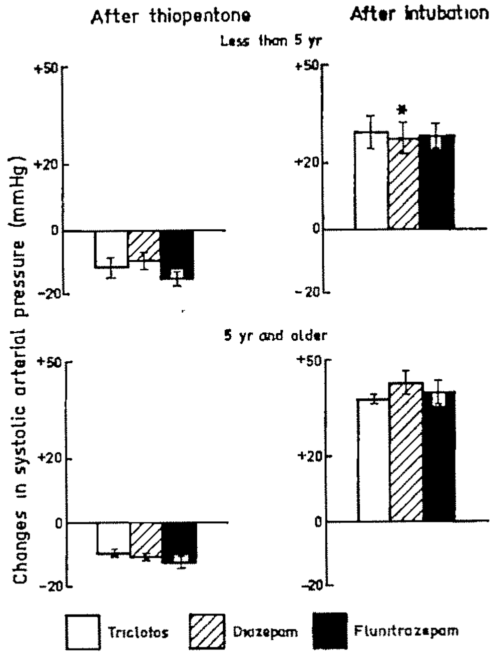


FIG. 2. Changes in arterial systolic pressure (±SEM) immediately after injection of thiopentone and 30 s after tracheal intubation. In different groups the mean initial values for arterial systolic pressures ranged from 107 to 125 mm Hg. Significant difference from the corresponding group of children 5 yr and older: $^*P<0.01$.

Figure 3 shows that there was no significant difference between the groups in terms of volume of gastric contents. Neither did the groups who were premedicated orally differ significantly from the

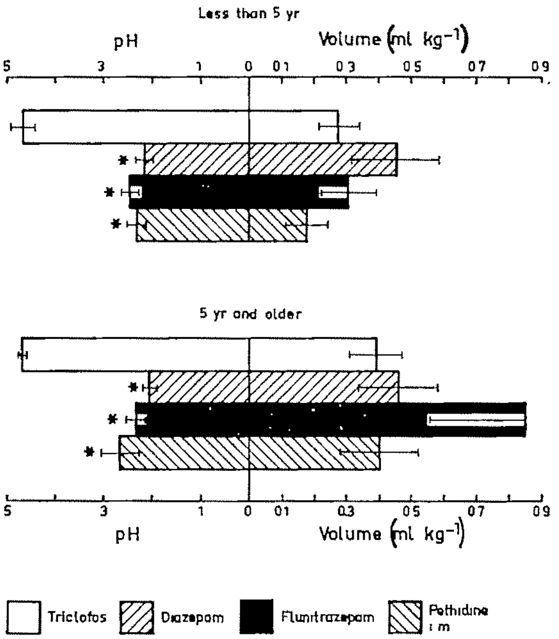


FIG. 3. Volume and pH of gastric fluid in different groups. Mean values ± SEM for 16–28 children. Significant difference from the corresponding triclofos group: $^{*}P < 0.001$.

i.m. pethidine groups. The mean pH of 4.5 after triclofos was significantly greater than the mean pH of 2.2 after the other drugs ($P < 0.001$).

One 8-yr-old girl premedicated with flunitrazepam vomited after induction before tracheal intubation. The hazard of aspiration was avoided by turning the patient to the lateral position followed by immediate suction of the oral cavity. The volume of the vomit was 200 ml (pH 3.5).

TABLE V. *Concentrations of diazepam and flunitrazepam in serum after oral administration. Mean values ± SEM. Number of children in parentheses. Significant difference from children less than 5 yr:* $^{*}P < 0.02$. *Significant difference from the value at 96 ± 15(SD) min:* $^{**}P < 0.001$

Premedicant group	Concentration (ng ml⁻¹) 96 min	180 min
Diazepam 0.25 mg kg⁻¹		
Less than 5 yr (18)	126.1 ± 18.8	99.4 ± 10.4
Older than 5 yr (24)	164.4 ± 13.9	144.6 ± 13.9*
Flunitrazepam 0.02 mg kg⁻¹		
Less than 5 yr (18)	5.6 ± 1.3	3.3 ± 0.8
Older than 5 yr (32)	6.4 ± 0.4	3.7 ± 0.3**

Table V shows that, 180 min after administration, the concentration of diazepam in the older children was significantly greater than in the younger ones ($P < 0.02$). There were no other significant differences between the two age groups, although the concentrations of both benzodiazepines in the older age group tended to be greater than in the younger one. The concentrations of both benzodiazepines decreased in a time-dependent manner.

DISCUSSION

Our results show that oral triclofos provided good anxiolysis in children less than 5 yr and that the effect of oral benzodiazepines was inferior to that of triclofos in this age group. All the premedicants, however, provided a good anxiolysis in the children 5 yr and older. The volume of gastric contents did not differ significantly between groups, whereas the gastric fluid was less acidic after triclofos than after the benzodiazepines or pethidine.

Anxiolytic effect

Our present results with triclofos agree well with the results obtained by Boyd and Manford (1973) who found triclofos to be a satisfactory oral premedicant for children aged 2–9 yr. In our present study diazepam given orally had a significantly better anxiolytic effect than when given i.m. as in our previous study (Lindgren, Saarnivaara and Himberg, 1979). It has been shown that the absorption of diazepam is better from the gastrointestinal tract than from muscle (Assaf, Dundee and Gamble, 1975; Kanto, 1975). This view may also be supported by our present results which show that at approximately 90 min and especially at 180 min after administration, the concentration of diazepam in serum was greater when given orally than when given i.m. as in our previous study (Lindgren, Saarnivaara and Himberg, 1979). Therefore, the different anxiolytic effect of diazepam in our studies may be the result of different concentrations of diazepam in serum.

In contrast to the superiority of flunitrazepam to diazepam in our previous study, flunitrazepam in the present study was inferior to diazepam in the younger age group. The poor effect of flunitrazepam does not seem to be the result of its poor absorption from the gastrointestinal tract, since the concentration of flunitrazepam was greater when given orally than when given i.m. Our results with oral flunitrazepam do not confirm the results obtained by Rouge and Gemperle (1975) who found that oral flunitrazepam is a good anxiolytic premedicant for children. The results of the studies, however, are not comparable since the dose (0.1 mg kg^{-1}) used by Rouge and Gemperle (1975) was five times the dose used by us.

Induction characteristics

In all premedicant groups, induction of anaesthesia was more often peaceful in the older children than in the younger ones. Furthermore, triclofos in the younger children caused a more tranquil induction than did flunitrazepam. Our present results confirm our earlier results (Lindgren, Saarnivaara and Himberg, 1979) that good anxiolysis before operation is followed by a peaceful induction. In both age groups, flunitrazepam prevented the fasciculations caused by suxamethonium more effectively than did diazepam. This finding confirms our earlier result (Lindgren, Saarnivaara and Himberg, 1979) in the older age group, but not in the younger in whom the fasciculations caused by suxamethonium were similar after diazepam and flunitrazepam. At induction of anaesthesia, the serum concentrations of flunitrazepam in our earlier and present studies were 3.1 and 5.6 ng ml^{-1}, respectively. Therefore, the greater preventive effect of flunitrazepam in the present study may be the result of a larger serum concentration compared with the earlier study although there was no positive correlation between the anxiolytic effect of flunitrazepam and its serum concentration.

Heart rate and antisialagogue effect

After arrival in the operating room, the heart rate in the older children was significantly less after the benzodiazepines than after triclofos. This difference does not seem to be the result of the better anxiolytic effect of the benzodiazepines compared with triclofos, since the anxiolytic effects of all drugs were similar in the older children. The increased heart rate following triclofos may be the result of its possible anticholinergic effect. This view is supported by the finding that triclofos also had a better antisialagogue effect than the benzodiazepines, especially flunitrazepam. This finding agrees well with that obtained by Boyd and Manford (1973), who found that, in combination with the same dose of atropine as in the present study, triclofos had a better antisialagogue effect than diazepam. Our results suggest that the younger children receiving flunitrazepam may need a larger dose of atropine than the other children. Mirakhur (1978) has shown that the ratio of oral to i.m. doses of atropine on salivary secretion and heart rate is 2 : 1 in adults. Our present results indicate that, in the younger flunitrazepam group, the dose ratio 2 : 1 might be better than the corresponding ratio 1.5 : 1 used by us. Furthermore, these children may even need an oral dose of 0.9 mg kg^{-1} of atropine as recommended by Binning and others (1962), who found this dose of atropine to have a satisfactory antisialagogue effect. Wyant and Kao (1974) and Mirakhur, Dundee and Clarke (1977) have found that glycopyrrolate is a more effective antisialagogue than atropine.

The volume and pH of gastric contents

The volume of gastric contents did not differ significantly between groups. The mean pH of 4.5 after triclofos was significantly greater than that of 2.2 after other drugs. Aspiration of gastric contents is a major hazard of anaesthesia (Bannister and Sattilaro, 1962; Salem, Wong and Collins, 1973). Aspiration pneumonitis is most likely when the pH of the aspirated fluid is less than 2.5 and the volume exceeds about 0.4 ml kg^{-1} (Teabeaut, 1952; Bannister and Sattilaro, 1962; Salem, Wong and Collins, 1973; Roberts and Shirley, 1974). On this basis, triclofos seems to be adequate and safer than diazepam or flunitrazepam or even i.m. pethidine. Anticholinergic drugs suppress acidic secretions in the stomach (Bachrach, 1964). Therefore, the superiority of triclofos may be the result of anticholinergic effects. Benzodiazepines may be as safe as triclofos when used in combination with a greater dose of atropine than was used in the present study or with another anticholinergic drug like glycopyrrolate which selectively inhibits the secretion of gastric acid and reduces the gastric contents (Salem, Wong and Collins, 1973; Salem et al., 1976; Baraka et al., 1977). Keating, Black and Watson (1978), however, were unable to reproduce these findings.

Concentration of benzodiazepines in serum

Our present results with oral benzodiazepines confirm our earlier results (Lindgren, Saarnivaara and Himberg, 1979), the results of Klotz and others (1975), and Korttila and others (1978) that the pharmacokinetics of diazepam and flunitrazepam are age-dependent.

ACKNOWLEDGEMENTS

We wish to thank F. Hoffmann–La Roche & Co. Ltd for generous supplies of flunitrazepam. We are very grateful to Miss Aini Mikkonen, Mrs Liisa Leppänen, Mrs Riitta Pietikäinen, Miss Kristiina Karjalainen, Mrs Marja-Leena Michelsson, Mrs Pirjo Torkkeli and Mrs Marja-Leena

Ylinen and to the personnel of the recovery room and of the ward for their skilful assistance during this study. Our thanks are due to Miss Elizabeth Heap for final checking of the English language. This work was supported by the Paulo Foundation, Finland.

REFERENCES

Assaf, R. A. F., Dundee, J. W., and Gamble, J. A. S. (1975). The influence of the route of administration on the clinical action of diazepam. *Anaesthesia*, **30**, 152.

Bachrach, W. H. (1964). Anticholinergic drugs: survey of the literature and some experimental observations. *Am. J. Dig. Dis.*, **9**, 706.

Bannister, W. K., and Sattilaro, A. J. (1962). Vomiting and aspiration during anesthesia. *Anesthesiology*, **23**, 251.

Baraka, A., Saab, M., Salem, M. R., and Winnie, A. P. (1977). Control of gastric acidity by glycopyrrolate premedication in the parturient. *Anesth. Analg.* (*Cleve.*), **56**, 642.

Barker, R. A., and Nisbet, H. I. A. (1973). The objective measurement of sedation in children: a modified scoring system. *Can. Anaesth. Soc. J.*, **5**, 599.

Binning, R., Watson, W. R., Samrah, M., and Martin, E. (1962). Premedication for adenotonsillectomy. *Br. J. Anaesth.*, **34**, 812.

Boyd, J. D., and Manford, L. M. (1973). Premedication in children. *Br. J. Anaesth.*, **45**, 501.

Kanto, J. (1975). Plasma concentrations of diazepam and its metabolites after peroral, intramuscular and rectal administrations. Correlation between plasma concentration and sedatory effect of diazepam. *Int. J. Clin. Pharmacol.*, **12**, 427.

Keating, P. J., Black, J. F., and Watson, D. W. (1978). Effects of glycopyrrolate and cimetidine on gastric volume and acidity in patients awaiting surgery. *Br. J. Anaesth.*, **50**, 1247.

Klotz, U., Avant, G. R., Hoyumpa, A., Schenker, S., and Wilkinson, G. R. (1975). The effect of age and liver disease on the disposition and elimination of diazepam in adult man. *J. Clin. Invest.*, **55**, 347.

Korttila, K., Saarnivaara, L., Tarkkanen, J., Himberg, J.-J., and Hytönen, M. (1978). Effect of age on amnesia and sedation induced by flunitrazepam during local anaesthesia for bronchoscopy. *Br. J. Anaesth.*, **50**, 1211.

Lindgren, L., Saarnivaara, L., and Himberg, J.-J. (1979). Comparison of i.m. pethidine, diazepam and flunitrazepam as premedicants in children undergoing otolaryngological surgery. *Br. J. Anaesth.*, **51**, 321.

Mirakhur, R. K. (1978). Comparative study of the effects of oral and i.m. atropine and hyoscine in volunteers. *Br. J. Anaesth.*, **50**, 591.

—— Dundee, J. W., and Clarke, R. S. J. (1977). Glycopyrrolate–neostigmine mixture for antagonism of neuromuscular block: comparison with atropine–neostigmine mixture. *Br. J. Anaesth.*, **49**, 825.

Roberts, R. B., and Shirley, M. A. (1974). Reducing the risk of acid aspiration during Cesarean section. *Anesth. Analg.* (*Cleve*), **53**, 859.

Rouge, J.-C., and Gemperle, G. N. (1975). Le Rohypnol en chirurgie pédiatrique; in *Bisherige Erfahrungen mit "Rohypnol" (Flunitrazepam) in der Anästhesiologie und Intensivtherapie* (eds W. Hügin, G. Hossli and M. Gemperle), p. 169. Basel: Editiones "Roche", Basel.

Salem, M. R., Wong, A. Y., and Collins, V. J. (1973). The pediatric patient with a full stomach. *Anesthesiology*, **39**, 435.

—— —— Mani, M., Bennett, E. J., and Toyama, T. (1976). Premedicant drugs and gastric juice pH and volume in pediatric patients. *Anesthesiology*, **44**, 216.

Teabeaut, J. R. (1952). Aspiration of gastric contents. *Am. J. Pathol.*, **28**, 51.

Wyant, G. M., and Kao, E. (1974). Glycopyrrolate methobromide. I: Effect on salivary secretion. *Can. Anaesth. Soc. J.*, **21**, 230.

COMPARIASON DU TRICLOFOS, DU DIAZEPAM ET DU FLUNITRAZEPAM ADMINISTRES PAR VOIE BUCCALE EN TANT QUE PREMEDICATIONS A DES ENFANTS DEVANT SUBIR UNE INTERVENTION OTO-RHINO-LARYNGOLOGIQUE

RESUME

On a comparé au cours d'une étude à double inconnue effectuée sur 128 enfants devant subir une intervention oto-rhino-laryngologique les effets de l'administration buccale, en tant que prémédication, de triclofos à raison de 70 mg kg^{-1}, de diazépam à raison de 0,25 mg kg^{-1} et de flunitrazépam à raison de 0,02 mg kg^{-1}, en combinaison avec de l'atropine, elle-même à raison de 0,03 mg kg^{-1}. Tous ces agents ont assuré une bonne anxiolyse chez les enfants âgés de 5 ans et plus. Sur les enfants de moins de cinq ans, les effets du triclofos ont été plus forts que ceux du diazépam et du flunitrazépam. Il y a eu une corrélation positive entre l'anxiolyse et la facilité avec laquelle l'anesthésie a été provoquée. Dans les deux groupes d'âge, le flunitrazépam a empêché les fasciculations causées par le suxaméthonium, d'une manière plus efficace que le diazépam ou le triclofos. La fréquence cardiaque avant l'induction, mais après l'administration de triclofos, a été plus forte qu'après l'administration des autres agents et son effet antisialagogue a été plus fort. Le volume moyen du contenu gastrique a été de 0,4 ml kg^{-1} pour tous les patients et il n'y a eu aucune différence statistique entre les groupes. Le pH moyen du contenu gastrique a été de 4,5 après le triclofos et de 2,2 après les autres agents. Les concentrations dans le sérum des deux benzodiazépines dans le groupe le plus âgé ont été plus fortes que dans le groupe le plus jeune.

VERGLEICH VON TRICLOFOS, DIAZEPAM UND FLUNITRAZEPAM ALS ORAL VERABREICHTES VORBEHANDLUNGSMITTEL FÜR KINDER BEI OTOLARYNGOLOGISCHEN EINGRIFFEN

ZUSAMMENFASSUNG

Triclofos 70 mg kg^{-1}, Diazepam 0,25 mg kg^{-1} und Flunitrazepam 0,02 mg kg^{-1} in Kombination mit Atropin 0,03 mg kg^{-1} wurden als orales Vorbehandlungsmittel an 128 Kindern in einer Doppelblind-Studie verglichen—die Kinder erfuhren otolaryngologische Eingriffe. Alle Drogen bewirkten gute Anxiolyse bei Kindern von 5 Jahren und darüber. Bei Kindern unter 5 Jahren erwies sich Triclofos den beiden anderen Drogen als überlegen. Es bestand eine positive Korrelation zwischen Anxiolyse und der Leichtigkeit der Narkoseeinleitung. Bei beiden Altersgruppen

wurde die durch Suxamethonium verursachte Strangbildung durch Flunitrazepam wirksamer verhindert als durch die beiden anderen Drogen. Die Herztätigkeit vor der Narkose war nach Triclofos stärker als nach den anderen Drogen, und die antisialogische Wirkung von Triclofos war ebenfalls besser. Das mittlere Volumen des gastrischen Gehaltes war bei allen Patienten 0,4 mg kg^{-1}, ohne statistisch wesentliche Unterschiede zwischen den beiden Gruppen. Das mittlere pH des gastrischen Gehaltes betrug 4,5 nach Triclofos, und 2,2 nach den anderen Drogen. Die Serumkonzentration beider Benzodiazepine war bei den älteren Kindern höher als in der jüngeren Gruppe.

COMPARACION DE TRICLOFOS, DIAZEPAM Y FLUNITRAZEPAM ORALES COMO PREMEDICACION EN NIÑOS SOMETIDOS A CIRUJIA OTOLARINGOLOGICA

SUMMARIO

Se llevó a cabo una comparación de 70 mg kg^{-1} de triclofos, 0,25 mg kg^{-1} de diazepam y 0,02 mg kg^{-1} de flunitrazepam, cada uno en combinación con 0,03 mg kg^{-1} de atropina, usados como premedicación en 128 niños sometidos a cirujía otolaringológica en un estudio doble-ciego. Todas las sustancias proveyeron una buena ansíolisis en niños de 5 años o más. En niños de menos de 5 años, el triclofos tuvo efectos mayores a los del diazepam y del flunitrazepam. Hubo una correlación positiva entre la ansíolisis y la facilidad de inducción de la anestesia. En ambos grupos de edades, el flunitrazepam impidió las fasciculaciones causadas por el suxametonio de manera más eficaz que el diazepam o el triclofos. El ritmo cárdiaco de preinducción fue mayor después del triclofos que después las dos otras drogas y su efecto antisialógogo mayor. El volumen medio del contenido gástrico era de 0,4 ml kg^{-1} para todos los pacientes y no hubo ninguna diferencia estadísticamente significativa entre los grupos. El pH medio del contenido gástrico era de 4,5 después del triclofos y de 2,2 con las demás sustancias. La concentración en el suero de ambas benzodiazepinas fue mayor en el grupo de mayor edad que en el grupo de menor edad.

Br. J. Anaesth. (1980), **52**, 291

COMPARATIVE STUDY OF ATROPINE AND GLYCOPYRROLATE ON SUXAMETHONIUM-INDUCED CHANGES IN CARDIAC RATE AND RHYTHM

D. A. COZANITIS, J. W. DUNDEE AND M. M. KHAN

SUMMARY

The effectiveness of atropine and glycopyrrolate in the prophylaxis of suxamethonium-induced bradycardia was evaluated in a double-blind study of 56 patients. Three had clinically demonstrable bradycardia, all having received atropine. We conclude that glycopyrrolate offered adequate protection against cardiac effects of repeated doses of suxamethonium.

In 1958, Martin reported that suxamethonium-induced bradycardia could be reduced by the use of atropine as a premedicant. Bullough (1959) condemned the practice of giving repeated doses of suxamethonium unless a minimum of 0.65 mg of atropine had been administered. Lupprian and Churchill-Davidson (1960) confirmed that atropine could prevent bradycardia when given in a dose of 1 mg i.v. before the second dose of suxamethonium.

Glycopyrrolate, an antimuscarinic agent, has been evaluated extensively recently (Klingenmaier et al., 1972; Mirakhur, Dundee and Clarke, 1977; Cozanitis et al., 1980). There is, however, no evidence that it prevents changes in heart rate and rhythm associated with suxamethonium. Therefore we have compared the efficacy of atropine and glycopyrrolate on suxamethonium-induced cardiac effects.

PATIENTS AND METHODS

Fifty-six patients about to undergo minor surgery were studied. All were premedicated orally approximately 1 h before induction of anaesthesia with either diazepam 5–10 mg or meprobamate 800 mg. Two minutes before induction, they received either glycopyrrolate 0.005 mg kg^{-1} or atropine 0.01 mg kg^{-1} into an i.v. infusion of a physiological electrolyte solution. Allocation to the study drugs was randomized and double-blind.

The induction of anaesthesia, following a 2-min period of oxygenation, was with a sleep-dose of thiopentone, demonstrated by loss of the eyelash reflex. Suxamethonium 1 mg kg^{-1} was given i.v. to facilitate tracheal intubation. Anaesthesia was maintained with 33% oxygen in nitrous oxide, with 25–50-mg increments of thiopentone, when necessary. A peripheral nerve stimulator (Wellcome) was applied to the bridge of the nose at intervals and on return of the contractions of the orbicularis oculi, a second and third dose of suxamethonium 0.5 mg kg^{-1} were given. Monitor chest leads were used to record a single-channel electrocardiogram (e.c.g.) at intervals throughout the study. Atropine was always immediately available for use in case of severe and sustained decrease of heart rate. At the end of the study period, the planned surgical procedure was carried out.

The number of patients showing bradycardia, as defined by a heart rate less than 55 beat min^{-1}, was determined. Mean heart rate was measured by averaging 10 R–R intervals, 30 s after the administration of the antimuscarinic agent and similarly following thiopentone. If a wide fluctuation of heart rate occurred, the range was recorded and the mean heart rate was measured during the following 30 s. Heart rate was determined every 15 s after each increment of suxamethonium. Changes in cardiac rhythm were recorded.

The split-plot analysis of variance and the Mann–Whitney *U* test were used for statistical analysis when appropriate.

RESULTS

Table I shows some relevant details of the patients. The mean weight in the glycopyrrolate series was less

---

DEMITRI A. COZANITIS,* B.SC.PHARM., M.D., D.T.M.H.; JOHN W. DUNDEE, M.D., PH.D., F.F.A.R.C.S., M.R.C.P.; Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland. MAZHAR M. KHAN, M.B., B.S., M.R.C.P., Department of Cardiology, Royal Victoria Hospital, Belfast.

* Present address: Department of Anaesthesia, University Central Hospital, 00290 Helsinki 29, Finland.

0007–0912/80/030291–03. $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Some details of the patients studied*

	Atropine	Glycopyrrolate
Number of patients	28	28
Mean age ± SEM (yr)	39 ± 2.4	40 ± 2.2
Mean weight ± SEM (kg)	65 ± 1.9	57 ± 2.2
Males	12	5
Mean time ± SEM (min)		
Study drug–1st sux. dose	3.9 ± 0.15	3.9 ± 0.16
1st sux. dose–2nd dose	3.6 ± 0.23	3.9 ± 0.23
2nd sux. dose–3rd dose	3.6 ± 0.8	3.3 ± 0.29

than that of those having received atropine because of a greater proportion of females in the former group. There were no major differences in the times between administration of the study drugs and the first administration of suxamethonium and between the subsequent doses of suxamethonium.

Both drugs produced an increase in heart rate of about 10 beat min^{-1} after administration, but this change was neither clinically nor statistically significant. Indeed, there were no statistically significant differences in the mean heart rates between the two series at any time (fig. 1).

No patient developed bradycardia following the first dose of suxamethonium but the second dose did result in bradycardia in three patients, all in the atropine series. Bradycardia was seen in two of these patients again after the third suxamethonium dose. The bradycardia always developed within 45 s of injection of the suxamethonium and was transient, the heart rate reverting to pre-suxamethonium values within 75 s.

In those patients with clinically significant bradycardia, one patient had sinus arrest lasting 3.2 s after the second increment of suxamethonium and another episode of sinus arrest of 2.2 s following the third dose of the relaxant. One patient developed nodal bradycardia while another showed sinus bradycardia. A further five patients had e.c.g. abnormalities; four of these were in the atropine series—two presented with nodal rhythm, one had atrial ectopic beats and one, ventricular extrasystoles. The fifth patient, in the glycopyrrolate series, had nodal rhythm after administration of this antimuscarinic agent and during induction with thiopentone.

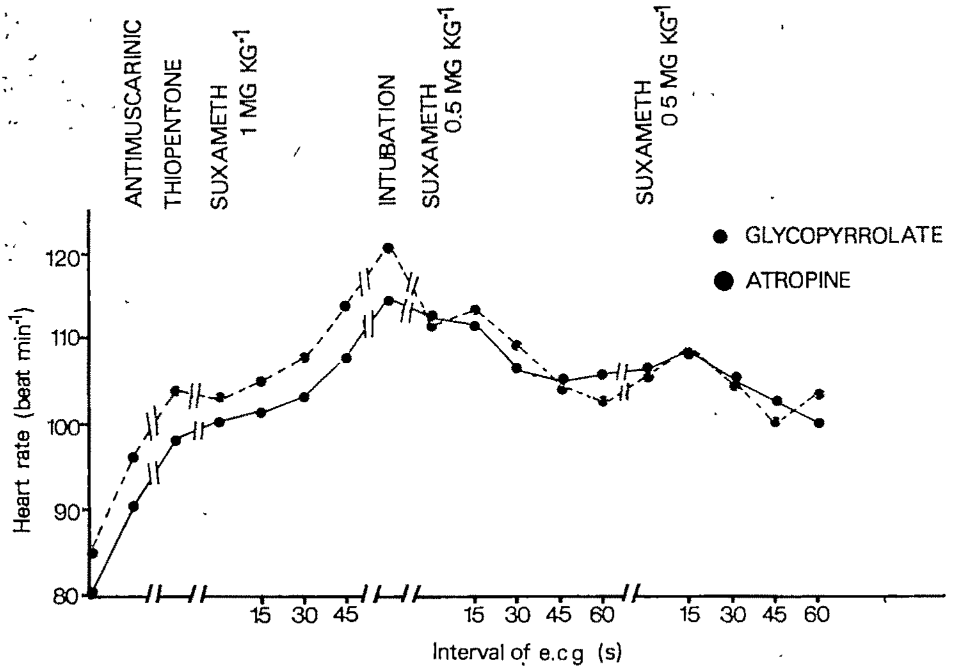


FIG. 1. Changes of mean heart rates of the patient series at the different intervals of the study period.

DISCUSSION

The results show that, although bradycardia occurred in three of the patients receiving atropine following the subsequent doses of suxamethonium as compared with none in the glycopyrrolate series, the mean heart rate changes in the two groups were not statistically significant. It is important to note that clinically significant decreases in heart rate occurred in three patients even though they had been pretreated with i.v. atropine immediately before the induction of anaesthesia.

An interesting observation was made on the cardiac rhythm of two patients, one from each series, who developed nodal rhythm after the i.v. injection of the antimuscarinic study drug. It appears that, initially, antimuscarinics cannot drive the sinus node but influence the A–V junctional node, but later the sinus node begins to take over. Neither of these patients showed any evidence of sinus node dysfunction in the resting e.c.g.

One patient developed sinus arrest lasting 3.2 s after the second dose of suxamethonium, and this occurred again for 2.2 s, following the third increment of suxamethonium. Nodal bradycardia followed these episodes. It appears that this is a result of the parasympathetic effect of the relaxant on the sinus node.

It is apparent from this study that glycopyrrolate offers protection against the cardiac effects resulting from intermittent administration of suxamethonium similar to or greater than that of atropine. One could argue that a controlled study using a series of patients not having received any antimuscarinic medication is necessary before the absolute efficacy of these two drugs can be evaluated. However, this possibility was discounted as being unethical.

ACKNOWLEDGEMENT

A. H. Robins Co. Ltd provided the double-blind supplies of both atropine and glycopyrrolate. We thank Mr C. J. Jones, B.PHARM., for his assistance and encouragement in this study.

REFERENCES

Bullough, J. (1959). Intermittent suxamethonium injections. *Br. Med. J.*, **1**, 786.

Cozanitis, D. A., Dundee, J. W., Merrett, J. D., Jones, C. J., and Mirakhur, R. K. (1980). Evaluation of glycopyrrolate and atropine as adjuncts to reversal of non-depolarizing neuromuscular blocking agents in a "true-to-life" situation. *Br. J. Anaesth.*, **52**, 85.

Klingenmaier, C. H., Bullard, R., Thompson, D., and Watson, R. (1972). Reversal of neuromuscular blockade with a mixture of neostigmine and glycopyrrolate. *Anesth. Analg. (Cleve.)*, **51**, 468.

Lupprian, K. L., and Churchill-Davidson, H. C. (1960). Effect of suxamethonium on cardiac rhythm. *Br. Med. J.*, **2**, 1774.

Martin, K. H. (1958). International Symposium on Curare and Curare-like drugs. *Atti XI Congr. Soc. Ital. Anestesiol.* Venice, September 1958, p. 362.

Mirakhur, R. K., Dundee, J. W., and Clarke, R. S. J. (1977). Glycopyrrolate–neostigmine mixture for antagonism of neuromuscular block: comparison with atropine–neostigmine mixture. *Br. J. Anaesth.*, **49**, 825.

ETUDE COMPARATIVE DE L'ATROPINE ET DU GLYCOPYRROLATE EN CE QUI CONCERNE LES MODIFICATIONS DUES AU SUXAMETHONIUM DU RYTHME ET FONCTION CARDIAQUES

RESUME

On a procédé à l'évaluation au moyen d'une étude à double inconnue sur 56 patients de l'efficacité de l'atropine et du glycopyrrolate dans la prophylaxie de la bradycardie provoquée par le suxaméthonium. Trois patients souffraient de bradycardie cliniquement évidente et tous avaient reçu de l'atropine. Nous en avons conclu que le glycopyrrolate offre une protection adéquate contre les effets cardiaques de doses réitérées de suxaméthonium.

VERGLEICHENDE STUDIE VON ATROPIN UND GLYCOPYROLAT BEI DURCH SUXAMETHONIUM BEWIRKTE VERÄNDERUNGEN VON HERZTÄTIGKEIT UND RHYTHMUS

ZUSAMMENFASSUNG

Die Wirksamkeit von Atropin und Glycopyrolat in der Prophylaxe von durch Suxamethonium bewirkte Bradykardie wurde in einer Doppelblind-Studie mit 56 Patienten untersucht. Drei davon hatten eine klinisch demonstrierbare Bradykardie, nachdem sie Atropin erhalten hatten. Wir schlossen daraus, dass Glycopyrrolat einen ausreichenden Schutz gegen die Auswirkungen wiederholter Dosen von Suxamethonium auf die Herztätigkeit bietet.

ESTUDIO COMPARATIVO DE LA ATROPINA Y DEL GLICOPIRROLATO SOBRE LOS CAMBIOS INDUCIDOS POR SUXAMETONIO EN EL RITMO CARDIACO Y FUNCION SISTOLICA

SUMARIO

Se procedió a la evaluación de la eficacia de la atropina y del glicopirrolato en la profilaxis de la bradicardia inducida por suxametonio en el curso de un estudio doble-ciego de 56 pacientes. Tres de ellos padecieron de bradicardia clínicamente demostrable, habiéndose administrado atropina a todos. Concluimos que el glicopirrolato ofrecía una protección adecuada contra los efectos cardíacos de repetetidas dosis de suxametonio.

Br. J. Anaesth. (1980), **52**, 295

A DOUBLE-BLIND COMPARISON OF MEPTAZINOL WITH PETHIDINE IN POSTOPERATIVE PAIN

A. HEDGES, P. TURNER AND J. WADSWORTH

SUMMARY

Three groups each of 24 patients who had undergone total abdominal hysterectomy were studied on the 1st day after operation. Under double-blind conditions, group 1 compared meptazinol 60 mg with pethidine 100 mg, group 2, meptazinol 75 mg with pethidine 100 mg and group 3, meptazinol 100 mg with pethidine 100 mg. The drugs were given i.m. Analgesic activity was assessed by patients rating their pain before and 1 h after the administration of each treatment and by patient and investigator preference for treatment. From the pain relief score, pethidine was not significantly better than any dose of meptazinol in relieving pain. Patients preferred pethidine 100 mg to meptazinol 60 mg ($P<0.01$, McNemar's test), but there was no significant difference between meptazinol and pethidine for observer or patient preference when the dose of meptazinol was increased to 75 mg or 100 mg.

Meptazinol ((m-3-ethyl-1-methylhexahydro-1-H-azapine-3-ylphenol) hydrochloride, Wyeth Laboratories) is an opioid antagonist drug with analgesic properties. Paymaster (1976, 1977) has shown that it produces significant pain relief in doses of 60–150 mg per 70 kg i.m. in patients recovering from abdominal surgery and, orally, meptazinol 400 mg was significantly better than placebo in relieving pain after operation in patients who had undergone total abdominal hysterectomy operations (Hedges et al., 1977). The i.v. administration of meptazinol was effective in relieving the pain of acute renal colic (Oosterlinck and de Sy, 1975).

The present study was carried out to evaluate the efficacy of three doses of meptazinol administered i.m., compared with pethidine, in relieving pain following surgery.

METHODS

Three groups, each of 24 female patients aged 27–64 yr who had undergone total abdominal hysterectomy, were studied. In group 1, meptazinol 60 mg was compared with pethidine 100 mg; in group 2, meptazinol 75 mg was compared with pethidine 100 mg and, in group 3, meptazinol 100 mg was compared with pethidine 100 mg. The informed consent of the patients to participate in the trial was obtained; all tests were carried out on the first day after operation. Patients were specifically excluded from the trial if they suffered from cardiac, pulmonary, renal or hepatic disease. The drugs were administered i.m. to the patients in a cross-over design under double-blind conditions in random order, according to an individual numerical code.

The analgesic efficacy of the two treatments was assessed by:

(a) interviewing the patients 1 h after they had received each injection;
(b) noting the times that the injections were administered and the time at the end of the trial when the next analgesic, either pethidine or papaveretum, was given;
(c) recording the side-effects of either treatment noted by the patient;
(d) the patients were asked by means of a multi-choice questionnaire (1) to rate their initial level of pain before the injection as "slight", "quite severe" or "as severe as I have ever felt it"; (2) to rate their pain relief 1 h after the injection as: not changed at all = 0, slight relief = 1, moderate relief = 2, almost complete relief = 3, complete relief = 4; and (3) to select their preference, if any, for either treatment.

From this, it was possible to obtain an investigator-preference for treatment by one of us (A. H.), based solely on the degree of pain relief, and a patient preference for treatment.

Statistical analysis

The patient and investigator preferences and the pain relief ratings were analysed using McNemar's test. Wilcoxon's matched pairs signed-ranks test was used to assess the significance of the difference of

---

ANNMARIE HEDGES, PH.D.; P. TURNER, M.D., F.R.C.P.; Department of Clinical Pharmacology, St Bartholomew's Hospital, London EC1A 7BE. JANE WADSWORTH, M.SC., Department of Medical Electronics, St Bartholomew's Hospital, London EC1A 7BE.

0007-0912/80/030295-04 $01.00

© Macmillan Journals Ltd 1980

the times between administration of the two treatments.

RESULTS

The patient and observer preferences for treatment in the three groups are shown in table I. Patient preference for pethidine 100 mg compared with meptazinol 60 mg was significant (McNemar's test, $\chi^2 = 7.6$, $P < 0.01$). However, when the dose of meptazinol was increased to 75 mg or 100 mg, there was no significant difference between meptazinol and pethidine 100 mg on patient or observer preference.

In table II, the pain relief scores are subdivided according to the initial pain experienced by the patients. Pethidine was not significantly better than any dose of meptazinol in relieving pain.

Although more patients had better pain relief scores after pethidine 100 mg than any dose of

TABLE I. *The number of patient and observer preferences for the two treatments in the three groups studied*

	Preference for pethidine	Preference for meptazinol	Both treatments the same
Patient preference			
Group 1			
Meptazinol 60 mg *v.* pethidine 100 mg	16	3	5
Group 2			
Meptazinol 75 mg *v.* pethidine 100 mg	7	4	13
Group 3			
Meptazinol 100 mg *v.* pethidine 100 mg	7	5	12
Observer preference			
Group 1	10	5	9
Group 2	10	4	10
Group 3	5	2	17

TABLE II. *Mean pain relief scores 1 h after pethidine and meptazinol in the three groups of patients studied*

Initial pain level	*n*	Pain relief score after meptazinol	*n*	Pain relief score after pethidine
Group 1: Meptazinol 60 mg *v.* pethidine 100 mg				
All levels	24	2.2	24	2.6
Slight	3	3.33	2	3.5
Quite severe	13	2.0	12	2.4
Severe	8	2.0	10	2.7
Group 2: Meptazinol 75 mg *v.* pethidine 100 mg				
All levels	24	2.33	24	2.75
Slight	0	—	1	3.0
Quite severe	15	2.4	15	2.93
Severe	9	2.22	8	2.38
Group 3: Meptazinol 100 mg *v.* pethidine 100 mg				
All levels	24	2.75	24	3.04
Slight	1	3.0	5	3.6
Quite severe	18	3.0	13	3.08
Severe	5	1.8	6	2.5

TABLE III. *The number and percentage of patients with better pain relief scores (PRS) after pethidine or meptazinol in the three groups of patients studied*

	PRS better after pethidine	PRS better after meptazinol	PRS same after both treatments
Group 1			
Meptazinol 60 mg *v.* pethidine 100 mg	11 45.83%	5 20.83%	8 33.33%
Group 2			
Meptazinol 75 mg *v.* pethidine 100 mg	10 41.67%	5 20.83%	9 37.5%
Group 3			
Meptazinol 100 mg *v.* pethidine 100 mg	7 29.17%	1 4.17%	16 66.67%

meptazinol (table III), this did not reach significance in any of the three groups.

In all three groups after pethidine or meptazinol administration there was no significant difference between the time until the next analgesic dose (table IV). The side-effects which were noted by the patients are listed in table V.

TABLE IV. *The median time (and range) after administration (min) of pethidine or meptazinol until the next analgesic dose in the three groups of patients studied*

Group 1	After meptazinol 60 mg 290 (185–555)	After pethidine 100 mg 275 (180–705)
Group 2	After meptazinol 75 mg 282.5 (205–435)	After pethidine 100 mg 267.5 (210–630)
Group 3	After meptazinol 100 mg 287.5 (235–535)	After pethidine 100 mg 282.5 (205–325)

TABLE V. *The side-effects noted by the patients in the three groups studied*

	Group 1: 7 of 24 patients reported side-effects	
Side-effect	Meptazinol 60 mg	Pethidine 100 mg
Nausea	1	1
Sweating	1	0
Dizziness	5	2
	Group 2: 12 of 24 patients reported side-effects	
	Meptazinol 75 mg	Pethidine 100 mg
Nausea	3	2
Sweating	2	1
Dizziness	3	4
Dry mouth	1	2
Blurred vision	1	2
Heartburn	1	0
	Group 3: 4 of 24 patients reported side-effects	
	Meptazinol 100 mg	Pethidine 100 mg
Nausea	3	0
Dizziness	1	2

DISCUSSION

The results of the present study confirm those of other workers (Paymaster, 1976, 1977) that meptazinol is an effective analgesic in pain after operation. Paymaster (1977) has shown that i.m. meptazinol 100 mg was equianalgesic with pethidine 100 mg in relieving pain following abdominal and orthopaedic surgery. Meptazinol 100 mg produced less sedation and had less adverse effects on lung function tests than pethidine 100 mg (Paymaster, 1977). The negligible depressant action of meptazinol on respiration was confirmed by Jordan and others (1979), who showed that meptazinol 100 mg per 70 kg, unlike morphine 20 mg per 70 kg or pentazocine 60 mg per 70 kg, had little effect on the slope and intercept of the ventilatory response to hypercapnia. The main side-effects associated with meptazinol in this study were nausea and dizziness, which have also been reported by other workers (Paymaster, 1977; Jordan et al., 1979). However, in all these studies, the frequency of side-effects was not greater in the meptazinol group than in the pethidine group.

If the finding in rats (Goode and White, 1971) and drug-addicted monkeys (Swain, Villancal and Seevers 1973) of the low-dependence factor for meptazinol is confirmed in man, meptazinol, as a potent analgesic with minimal respiratory depressant action, would be particularly useful when pain relief is required in patients with poor pulmonary function, in women during labour and during the period immediately after operation.

ACKNOWLEDGEMENTS

The authors thank Dr P. Robson, Wyeth Laboratories, for supplying the drugs used in the study and the surgeons and nursing staff of the gynaecological wards of St Bartholomew's Hospital for their co-operation.

REFERENCES

Goode, P. G., and White, A. C. (1971). Some properties of Wy 22811, a new analgesic compound. *Br. J. Pharmacol.*, **43**, 462.

Hedges, A., Rose, J., Leighton, M., and Turner, P. (1977). A double-blind comparison of meptazinol with placebo in post-operative pain. *J. Clin. Pharmacol.*, **17**, 125.

Jordan, C., Lehane, J. R., Robson, P. J., and Jones, J. G. (1979). A comparison of the respiratory effects of meptazinol, pentazocine and morphine. *Br. J. Anaesth.*, **51**, 497.

Oosterlinck, W., and de Sy, W. (1975). Preliminary clinical experience with meptazinol, a new analgesic. *Curr. Med. Res. Opin.*, **3**, 187.

Paymaster, N. J. (1976). Clinical evaluation of meptazinol, a new analgesic, in postoperative pain. *Br. J. Anaesth.*, **48**, 599.

—— (1977). Analgesia after operation. A controlled comparison of meptazinol, pentazocine and pethidine. *Br. J. Anaesth.*, **49**, 1139.

Swain, H. H., Villancal, J. E., and Seevers, M. H. (1973). Evaluation of new compounds for morphine-like physical dependence in the Rhesus monkey. *Committee on Problems of Drug Dependence*. 35th Meeting, Paper 55, Addendum 1, p. 693 (Natl. Acad. Sci.).

COMPARAISON A DOUBLE INCONNUE DU MEPTAZINOL ET DE LA PETHIDINE POUR LE SOULAGEMENT DES DOULEURS POSTOPERATOIRES

RESUME

Trois groupes comprennant chacun 24 malades qui avaient subi une hystérectomie totale ont fait l'objet d'études pendant la première journée qui a suivi l'intervention chirurgicale. Dans des conditions à double inconnue on a comparé, sur le groupe 1, 60 mg de meptazinol à 100 mg de péthidine; sur le groupe 2, 75 mg de meptazinol à 100 mg de péthidine et sur le groupe 3, 100 mg de meptazinol à 100 mg de péthidine. Les médicaments ont été injectés par voie intramusculaire. L'activité analgésique a été évaluée par les malades qui ont comparé la douleur qu'elles ressentaient avant l'injection et 1 h après l'administration de chaque traitement, puis par la malade et le chercheur en fonction de leur préférence pour le traitment. D'après la cote donnée au soulagement de la douleur, la péthidine n'a pas été sensiblement meilleure que n'importe quelle dose de meptazinol pour soulager la douleur. Les malades ont préféré 100 mg de péthidine à 60 mg de meptazinol ($P < 0{,}01$, test de McNemar), mais il n'y a eu aucune différence notoire entre le meptazinol et la péthidine en ce qui concerne la préférence de la malade ou de l'observateur lorsqu'on a augmenté la dose de meptazinol à 75 mg ou à 100 mg.

DOPPELBLINDVERGLEICH ZWISCHEN MEPTAZINOL UND PETHIDIN FÜR POSTOPERATIVE SCHMERZEN

ZUSAMMENFASSUNG

Drei Gruppen zu je 24 Patienten nach totaler Hysterektomie wurden am 1. Tag nach der Operation studiert. Unter Doppelblind-Bedingungen verglich Gruppe 1 eine Dosis von Meptazinol 60 mg mit Pethidin 100 mg, Gruppe 2, Meptazinol 75 mg mit Pethidin 100 mg und Gruppe 3 verglich Meptazinol 100 mg mit Pethidin 100 mg. Die Drogen wurden intramuskulär verabreicht. Schmerzlindernde Wirkungen wurden von den Patientinnen beurteilt, und zwar vor und eine Stunde nach Verabreichung der jeweiligen Dosen, sowie nach den Vorlieben von Patient und Arzt für die jeweilige Behandlung. Im Bezug auf Schmerzlinderung war Pethidin nicht wesentlich wirksamer als irgendeine Dosis von Meptazinol. Die Patientinnen zogen Pethidin 100 mg der Dosis von Meptazinol 60 mg vor ($P < 0{,}01$, McNemar-s Test), doch gab es zwischen den Drogen keine wesentlichen Unterschiede—weder für Patientinnen noch Ärzte—wenn die Dosis von Meptazinol auf 75 oder 100 mg erhoht wurde.

COMPARACION DOBLE-CIEGA DE MEPTAZINOL CON PETIDINA EN DOLORES POSTOPERATORIOS

SUMARIO

Se hizo un estudio el primer día después de la operacíon en tres grupos de 24 pacientes cada uno que se sometieron a una histerectomia abdominal total. En condiciones dobleciegas, se comparó en el Grupo 1 60 mg de meptazinol con 100 mg de petidina, en el Grupo 2, 75 mg de meptazinol con 100 mg de petidina y en el Grupo 3, 100 mg de meptazinol con 100 mg de petidina. Se administró las substancias i.m. Los pacientes procedieron a la evaluación de la actividad analgésica al tasar sus dolores antes y 1 h después de la administración de cada tratamiento y mediante la preferencia del paciente y del investigador respecto del tratamiento. En cuanto al alivio del dolor, la petidina no dió resultados significativamente mejores que cualquiera de las dosis de meptazinol para calmar los dolores. Los pacientes preferían 100 mg de petidina a 60 mg de meptazinol ($P < 0{,}01$, prueba de McNemar), pero no había diferencia significativa entre el meptazinol y la petidina para el observador ó el paciente cuando la dosis de meptazinol aumentó hasta 75 ó 100 mg.

Br. J. Anaesth. (1980), **52**, 299

FINE SCREEN FILTRATION OF BANKED BLOOD: EFFECT ON RED CELL SURVIVAL

J. D. BROWNING, I. C. M. GRAY AND I. MCA. LEDINGHAM

SUMMARY

Two fine screen mesh microfilters and the Baxter blood administration set commonly used in U.K. hospitals were compared for their effect on the red cell survival of transfused stored autologous blood in six healthy males. The effect of the filtered transfusions on pulmonary gas exchange and on blood coagulation was measured. No significant difference was found between either microfilter and the Baxter giving-set for the red cell survival of transfused blood. Pulmonary gas exchange and coagulation were unaffected by transfusion of one unit of whole blood. Post-transfusion bilirubin concentrations were significantly less with one of the microfilters compared with the Baxter giving-set, possibly because of trapping of effete red cells within the filter. An unsuspected finding was the effect of transfusion in increasing the peripheral blood neutrophil count.

Microfilters are used routinely in many centres during cardiopulmonary by-pass procedures and less frequently for massive transfusion of stored banked blood in an attempt to reduce the frequency of post-bypass or post-transfusion pulmonary insufficiency. Occlusion of pulmonary capillaries is thought to be caused by the micro-aggregates of debris known to be present in stored banked blood, or by released vasoconstrictor substances. A number of questions remain unanswered regarding the effect of microfilters on the blood traversing them. Does the relatively small pore size of the filter cause "invisible damage" to red cells, resulting in their early removal by the reticulo-endothelial system thus reducing the effectiveness of the transfusion? Does the large surface area of the microfilter produce activation of coagulation factors with the possible risk of inducing a consumptive coagulopathy?

Studies performed on patients undergoing bypass procedures or receiving massive blood transfusion are often difficult to interpret because of the large number of factors which may influence red cell survival, lung function and blood coagulation. We examined two fine screen mesh microfilters, the Pall Ultipor and the Biotest MF 10, and the Baxter blood administration set normally used in U.K. hospitals for their effect on the red cell survival of blood transfused through them and the effect of these transfusions on pulmonary gas exchange and blood coagulation in healthy male volunteers.

METHODS

Six healthy male volunteers (age range 22–50 yr) were studied; routine haematological and biochemical examination was performed to exclude any blood-losing conditions. By venesection 500 ml of blood was withdrawn with the assistance of the Glasgow and West of Scotland Blood Transfusion Service, the blood being collected into plastic double-pack blood storage bags containing CPD anticoagulant (Fenwal double pack FKR 1997). The blood was stored at 4 °C for 28 days, following which an aliquot was removed, labelled with chromium-51 and returned to the original unit of blood immediately before transfusion.

Transfusion was performed through one or other of the microfilters (both of which had integral administration sets) or through the Baxter blood administration set, in each case using an 18-gauge "Abbocath"-T cannula (Abbott Laboratories 4535–18) with gravity flow over 20–30 min. Following each transfusion the filter with attached giving set was removed from the empty blood pack and the residual blood allowed to transfuse under continuous supervision until the filter chamber had emptied. During each of the three phases of the study two filters of each type were used. Venous and arterial samples

---

J. D. BROWNING, M.B., CH.B., M.R.C.P. (UK), M.R.C.PATH., Haematology Laboratory, Law Hospital, Carluke, Lanarkshire ML8 5ER. I. C. M. GRAY, M.B., CH.B., F.R.C.S., Department of Orthopaedics, Western Infirmary, Glasgow, G11 6NT. I. MCA. LEDINGHAM, M.D. F.R.C.S.(ED.), Department of Surgery, Western Infirmary, Glasgow G11 6NT.

0007–0912/80/030299–06 $01.00

© Macmillan Journals Ltd 1980

were taken before and after transfusion to allow measurement of red cell survival, serum bilirubin, blood-gas tensions, coagulation studies, platelet count and full blood count.

The whole procedure, including venesection, transfusion and sampling, was performed on each volunteer on three separate occasions with 3 months between each phase, until all had received a transfusion through each of the three filters.

Filters

The Pall Ultipor is a fine screen mesh filter with a 40-μm pore size. The type used had an integral administration set (Pall Biomedical Limited SQ 40 KL).

The Biotest MF 10 is a multiple-layer fine screen mesh filter the pore sizes of the four different layers being 200, 50, 20 and 10 μm. This filter also had an integral administration set (Biotest Folex Ltd MF-10 B Lüer).

The Baxter administration set for blood and blood derivatives is widely used in hospitals throughout the U.K. and incorporates a filter with a 170-μm pore size (Travenol Laboratories Limited FKC 2055).

Red cell survival

After 28 days an aliquot of the stored blood was transferred, following thorough mixing, to the satellite pack of the Fenwal double pack which was separated after clipping. Twenty millilitre of this aliquot was labelled with 25 μCi of chromium-51 (Gray and Sterling, 1950) then returned to the original blood pack immediately before transfusion. Venous samples were taken from the volunteer at 5 min, 1, 2, 4 and 24 h after transfusion and then every 2nd or 3rd day for 3 weeks. The dose of radioactive label was reduced to 25 μCi in view of the measurement being performed three times on the same individual. To compensate for the reduced labelling, dose counting times were increased to 10 min. In the second and third phases of the study unlabelled samples from the units of stored blood and pre-transfusion samples from each volunteer were checked for residual activity from the previous phase.

Serum bilirubin concentration

This was measured before and 4 h after transfusion using a standard technique (Gambino and Schreiber, 1964).

Pulmonary gas exchange studies

All subjects lay supine for at least 20 min before arterial sampling. After infiltration of local anaesthetic immediately before and 1 h after transfusion arterial blood was sampled under anaerobic conditions into heparinized plastic syringes from the radial artery.

The samples were analysed immediately for $P\text{O}_2$, $P\text{CO}_2$, pH and base excess using a Radiometer ABL 1 blood-gas analyser. The measurements were corrected for the difference between the temperature of the electrodes and the subject's sublingual temperature, which was measured periodically. Alveolar–arterial $P\text{O}_2$ difference was calculated:

$$(P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}) = [P\text{I}_{\text{O}_2} - (P\text{a}_{\text{CO}_2}/0.8)] - P\text{a}_{\text{O}_2}$$

Coagulation studies

The Prothrombin Time (Dacie and Lewis 1975a). and the Partial Thromboplastin Time (Dacie and Lewis, 1975b) were measured on citrated samples obtained immediately before and at 5 min and 1 h after transfusion. The Partial Thromboplastin Time was measured also on a 50/50 mixture of test plasma and normal plasma.

Full blood count

These were performed using a Coulter Model S (Coulter Electronics Ltd) with differential counts performed manually on a 400 cell count. Platelets were counted using a modified Coulter ZF6 particle counter.

Statistics

Statistical analysis was performed using a two-way analysis of variance.

RESULTS

Red cell survival studies showed no significant difference between any of the filters used (table I). Measurements made during the first 24 h in order to detect any increased immediate red cell destruction showed a wide range of values for all three filters; no consistent differences were detectable between them. Serum bilirubin concentrations showed a marked and significant increase in all cases at 4 h after transfusion, but the increase was significantly less with the Biotest MF 10 filter than with the Baxter filter (table II).

There was no significant difference between the microfiltered and the non-microfiltered transfusion for $(P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2})$ difference (table III). Coagulation studies and platelet counts remained unaltered by the transfusions.

Table I. *Red cell half-life of transfused blood (days)*

Subject	Pall Ultipor	Baxter FKC 2055	Biotest MF 10
1	26	26.5	24
2	23	28	20
3	21	28	23
4	26	26	25
5	23	24	24
6	24	17	23
		$P>0.1$	

Table II. *Increase in serum bilirubin 4 h after transfusion (μmol litre^{-1})*

Subject	Pall Ultipor	Baxter FKC 2055	Biotest MF 10
1	32	47	24
2	15	20	15
3	18	18	21
4	23	24	15
5	22	27	16
6	55	63	50
		$0.05>P>0.01$	

Table III. *($P\text{A}_{\text{O}_2}-P\text{a}_{\text{O}_2}$) (mm Hg) before (A) and after (B) transfusion*

Subject	Age (yr)	Smoking (S)	Pall Ultipor		Baxter FKC 2055		Biotest MF 10	
			A	B	A	B	A	B
1	30	—	5.4	9.5	0.6	13.7	6.8	9.6
2	30	—	5.5	9.5	4.0	5.0	Not available	
3	34	—	2.0	10.1	−4.7	−2.5	7.9	8.7
4	50	S	26.9	23.5	25.9	30.6	28.5	26.2
5	22	S	8.0	7.8	3.9	3.9	5.3	10.7
6	42	—	2.5	11.6	10.9	10.7	17.3	7.7
			$P>0.1$		$P>0.1$		$P>0.1$	

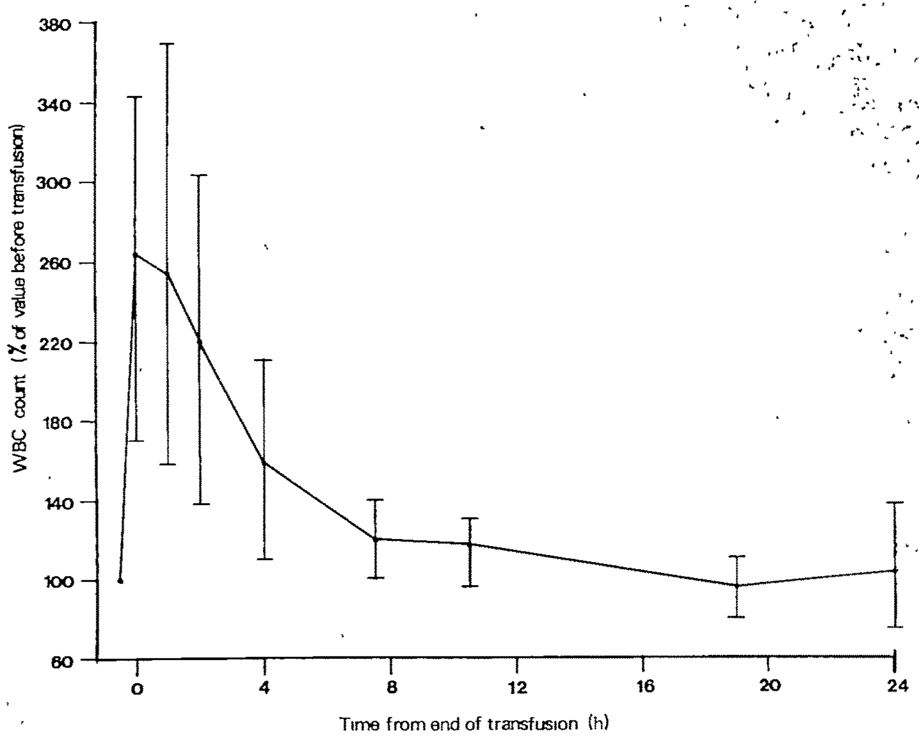


Fig. 1. Effect of transfusion of 500 ml of 4-week-old autologous blood on the peripheral white blood cell count (WBC). Mean and observed range for WBC as a percentage of pre-transfusion count shown against hours from the end of transfusion.

The white blood cell count was found to increase markedly immediately after transfusion in all volunteers in all three stages. From a value immediately after transfusion of approximately 2.5 times values before transfusion, the white cell count returned to normal over the ensuing 12 h (fig. 1).

DISCUSSION

Microaggregates of debris are found in stored banked blood (Swank, 1961; Solis et al., 1974). The clinical significance of this observation remains controversial. Many groups have suggested these microaggregates may cause problems with lung function and cerebral function if transfused in large numbers and that this problem can be reduced by removal of these aggregates by filtration (Jenevein and Weiss, 1964; Connell and Swank, 1973; Reul et al., 1973; Branthwaite, 1975). Virgilio and others (1977) showed no pulmonary problems following transfusion of stored blood with or without a microfilter. Whatever the truth of this controversy, filters are widely used.

Of the six filters at present available three are "depth" filters and utilize the fact that microaggregates are sticky and will adhere to filter elements made of dacron wool, polyurethane foam or polyester fibres. By having the blood pass through a considerable depth of element, these filters encourage multiple contacts of the aggregates with the surface in the hope that they will adhere and thus be removed (Guidoin, Gaylor and Borsanyi, 1976; Guidoin and Gilchrist, 1976; Marshall et al., 1978). Two of the six available filters, the Pall Ultipor and the Biotest MF 10, use fine screen mesh elements which trap aggregates mechanically, having a mesh with a pore size of suitable calibre. The remaining filter incorporates both depth and fine screen mesh elements (Marshall et al., 1976).

Many publications indicate that microfilters do not damage the elements of transfused blood. These reports have generally derived their results from *in vitro* or animal studies as determined by changes in plasma haemoglobin concentration (Dunbar, Price and Cannarella, 1974; Cullen and Ferrara, 1975). We attempted to show if, in the absence of damage to red cells causing haemolysis, there might be "invisible" damage resulting in their early removal by the reticulo-endothelial system. We are not aware of the sensitive technique of red cell survival being used previously in a study of this nature. Blood stored for 4 weeks was used as this duration of storage would increase the rigidity of the red cells (Mollison, 1974) and further increase the sensitivity of the investigation. Our results indicate that, under rapid gravity flow, no shortening of red cell survival could be demonstrated following transfusion through either microfilter although it should be noted that the blood transfused in our study was the first through each filter and these results may not hold for larger quantities. Furthermore, since both filters used in our study were of the fine screen mesh type no conclusions regarding the effect of the various depth filter elements can be drawn.

The initial decrease in radioactivity over the first 24 h showed a wide scatter of results and was not felt to be satisfactory in assessing the amount of red cell destruction occurring immediately after transfusion. However, the increase in serum bilirubin 4 h after transfusion gave figures related to the amount of haemoglobin metabolized immediately following transfusion (Mollison, 1974). The results show a significantly smaller increase in serum bilirubin following transfusion through the Biotest MF 10 filter than through the Baxter FKC 2055 filter, although differences between the Baxter and Pall filters and between the Pall and Biotest filters were not significant at the 5% level. We suggest this may be a result of mechanical trapping within the Biotest filter of effete red cells which, on storage, have "ballooned" to more than 10 µm diameter and which would normally be removed by the reticulo-endothelial system immediately after transfusion. The Pall Ultipor filter and the filter on the Baxter blood administration set have pore sizes well in excess of 10 µm diameter, and would not trap these cells so readily. With transfusion under pressure, however, these cells may be liable to break down in the filter (Haas, Blümell and Gathof, 1977).

It has been suggested that lung function may be compromised by massive transfusion of stored blood and protected by removal of aggregate debris with a microfilter (Ruel et al., 1973; Dawidson et al., 1975). Our results did not show any significant difference between values before and 1 h after transfusion for $(P\mathrm{A}_{\mathrm{O}_2}-P\mathrm{a}_{\mathrm{O}_2})$ with any of the filters tested.

Thrombus formation has been demonstrated on the elements of microfilters after transfusion of stored blood (Connell and Webb, 1975; Guidoin, 1976) and in view of the large surface area of the filter elements it is possible that activation of coagulation factors may occur even in the presence of an anticoagulant. Infusion of activated coagulation factors to a patient on bypass or receiving massive transfusion could possibly comprise an already active coagulation system with initiation of an intravascular coagulopathy. *In vitro* studies have not demonstrated any effect on coagulation (Gervin et al., 1973). Our studies were performed in an attempt to detect any coagulation abnormality induced by the transfusion or the filters. The 50/50 mixture of test and normal plasma was used to screen for early coagulation abnormalities where factor deficiencies are balanced by factor activation giving a normal partial thromboplastin time (PTT) result, but a shortened PTT when factor deficiencies are corrected by addition of normal plasma. No abnormalities were detected following transfusion through any of the filters used. The platelet count often decreases as an early indicator of a consumptive coagulopathy (Milligan et al., 1974) but in this study no significant decrease of the platelet count, even within the normal range, was found.

It was noted during the initial phase of the study that the peripheral blood white cell count immediately after transfusion was increased in all volunteers to about 2.5 times the value before transfusion. This was an unexpected finding although it has been noted previously (Huck, 1919). During subsequent phases of the study the same phenomenon was observed in all subjects with counts in some cases increasing to 20 000 white cells per μlitre and more. At no time during or immediately after transfusion did any of the volunteers show an increase in sublingual temperature. The leucocytosis was a result of an increase in neutrophils and settled to normal over the ensuing 12 h. In view of the significance often attached to an increased white blood cell count, we feel this observation is worthy of note. The explanation for the increase in white cell count is not clear but may represent the effect of a relatively rapid increase in circulating volume on the margination of neutrophils.

We feel that further observation of the effect of blood transfusion and microfilters on lung function and blood coagulation is indicated and that clarification of the effect of infusion on the white blood cell count would be of value.

ACKNOWLEDGEMENTS

We gratefully acknowledge the help of Dr A. W. Hutcheon in providing red cell survival results, the Glasgow and West of Scotland Blood Transfusion Service for their assistance with venesection, Mrs N. Haddow for secretarial help and Pall Biomedical Limited and Biotest Folex Limited for financial support.

REFERENCES

Branthwaite, M. A. (1975). Prevention of neurological damage during open-heart surgery. *Thorax*, **30**, 258.

Connell, R. S., and Webb, M. C. (1975). Filtration characteristics of three new in-line blood transfusion filters. *Ann. Surg.*, **181**, 273.

—— Swank, R. L. (1973). Pulmonary microembolism after blood transfusions: an electron microscopic study. *Ann. Surg.*, **177**, 40.

Cullen, D. J., and Ferrara, L. C. (1975). Fine-screen filtration of pressurized whole blood, packed cells and fresh-frozen erythrocytes. *Anesthesiology*, **43**, 578.

Dacie, J. V., and Lewis, S. M. (1975a). *Practical Haematology*, 5th edn, p. 331. Edinburgh: Churchill Livingstone.

—— —— (1975b). *Practical Haematology*, 5th edn, p. 337. Edinburgh: Churchill Livingstone.

Dawidson, I., Barrett, J. A., Miller, E., and Litwin, M. S. (1975). Pulmonary microembolism associated with massive transfusion. I: Physiologic effects and comparison *in vivo* of standard and dacron wool (Swank) blood transfusion filters in its prevention. *Ann. Surg.*, **181**, 51.

Dunbar, R. W., Price, K. A., and Cannarella, C. F. (1974). Microaggregate blood filters: effect on filtration time, plasma hemoglobin and fresh blood platelet counts. *Anesth. Analg. (Cleve.)*, **53**, 577.

Gambino, S. R., and Schreiber, H. (1964). *Technicon Symposium*, Paper 54. New York: Technicon Corporation.

Gervin, A. S., Limbird, T. J., Puckett, C. L., and Silver, D. (1973). Ultrapore hemofiltration. *Arch. Surg.*, **106**, 333.

Gray, S. J., and Sterling, K. (1950). The tagging of red cells and plasma proteins with radioactive chromium. *J. Clin. Invest.*, **29**, 1604.

Guidoin, R. (1976). Techniques of filter evaluation Part II; in *The Fine-screen Filtration of Stored Blood*, p. 49. Portsmouth: Pall Biomedical.

—— Gaylor, J. D. S., and Borsanyi, J. P. (1976). Banked blood microfiltration. I: Microfilter composed of five polyurethane foam layers with graded pore size. *Br. J. Haematol.*, **33**, 583.

—— Gilchrist, T. (1976). Banked blood microfiltration. II: Dacron–wool microfilter. *Br. J. Haematol.*, **33**, 591.

Haas, S., Blümel, G., and Gathof, A. G. (1977). The effect of the MF 10 filter on coagulation and on the corpuscular elements of the blood; in *The Microfiltration of Blood*, Special Edition No. 6, p. 37. Frankfurt-am-Main: Biotest-Serum-Instut GmbH.

Huck, J. G. (1919). Changes in the blood immediately following transfusion. *Bull. Johns Hopkins Hosp.*, **30**, 63.

Jenevein, E. P., and Weiss, D. L (1964). Platelet microemboli associated with massive blood transfusion. *Am. J. Pathol.*, **45**, 313.

Marshall, B. E., Wurzel, H. A., Neufeld, G. R., Aukburg, S. J., Ewing, B. C., Fried, R. J., and Barnes, C. (1978). Effects of Fenwal 4C2423 transfusion microfilter on microaggregates and other constituents of stored blood. *Transfusion*, **18**, 38.

—— —— —— Klineberg, P. L. (1976). Effects of Intersept micropore filtration of blood on microaggregates and other constituents. *Anesthesiology*, **44**, 525.

Milligan, G. F., MacDonald, J. A. E., Mellon, A., and Ledingham, I. McA. (1974). Pulmonary and hematologic disturbances during septic shock. *Surg. Gynecol. Obstet.*, **138**, 43.

Mollison, P. L. (1974). *Blood Transfusion in Clinical Medicine*, 5th edn, pp. 51, 556. Oxford: Blackwell.

Reul, G. J., Greenberg, S. D., Lefrak, E. A., McCollum, W. B., Beall, A. C., and Jordan, G. L. (1973). Prevention of post-traumatic pulmonary insufficiency. *Arch. Surg.*, **106**, 386.

Solis, R. T., Goldfinger, D., Gibbs, M. B., and Zeller, J. A. (1974). Physical characteristics of microaggregates in stored blood. *Transfusion*, **14**, 538.

Swank, R. L. (1961). Alterations of blood on storage: measurement of adhesiveness of "aging" platelets and leukocytes and their removal by filtration. *N. Engl. J. Med.*, **265**, 728.

Virgilio, R. W., Smith, D. E., Rice, C. L., Hobelmann, C. F., and Peters, R. M. (1977). To filter or not to filter? *Intens. Care Med.*, **3**, 153.

FILTRATION AU TAMIS FIN DE SANG PROVENANT DE BANQUES DU SANG: EFFET SUR LA SURVIVANCE DES GLOBULES ROUGES

RESUME

On a comparé deux microfiltres ayant des tamis à fines mailles et l'appareil de Baxter pour l'administration du sang que l'on utilise couramment dans les hôpitaux du Royaume-Uni, afin de déterminer leurs effets sur la survivance des globules rouges du sang autologue entreposé et transfusé à six sujets mâles en bonne santé. On a mesuré les effets des transfusions filtrées sur l'échange de gaz pulmonaire et sur la coagulation du sang. On n'a trouvé aucune différence importante entre le microfiltre et l'appareil de Baxter du point de vue survivance des globules rouges du sang transfusé. L'échange de gaz pulmonaire et la coagulation n'ont pas été affectés par la transfusion d'une unité de sang complet. Après la transfusion, les concentrations de bilirubine ont été nettement moindres avec l'un des microfiltres qu'avec l'appareil de Baxter, probablement à cause de la rétention à l'intérieur du filtre des globules rouges épuisés. Une découverte inattendue a été l'effet de la transfusion sur l'augmentation de la numération des neutrophiles du sang périphérique.

FEINSIEBFILTRIERUNG VON GESPEICHERTEM BLUT: AUSWIRKUNG AUF DAS ÜBERLEBEN DER ROTEN ZELLEN

ZUSAMMENFASSUNG

Zwei Feinsieb-Mikrofilter und das in britischen Krankenhäusern meistens verwendete Baxter Blutspeichergerat wurden im Bezug auf ihre Wirkung auf das Überleben der roten Zellen bei der Transfusion von gespeichertem autologem Blut in sechs gesunde männliche Versuchspersonen miteinander verglichen. Die Wirkung filtrierter Transfusionen auf den pulmonaren Gasaustausch und die Blutgerinnung wurde gemessen. Für das Überleben der roten Zellen des übertragenen Blutes bestand kein Unterschied zwischen Mikrofilter und Baxter-Gerat. Pulmonarer Gasaustausch und Gerinnung wurden durch die Transfusion einer Einheit Vollblut nicht beeinträchtigt. Die Bilirubin-Konzentrationen nach der Transfusion waren mit einem Mikrofilter wesentlich geringer als beim Baxter-Gerät—vielleicht wegen des Abfangens einiger roter Zellen im Filter. Ein unerwartetes Ergebnis war die Wirkung der Transfusion, die Anzahl der peripheren Blutneutrophilen zu erhöhen.

FILTRACION POR PANTALLA FINA DE SANGRE ALMACENADA EN BANCO: EFECTO SOBRE LA SUPERVIVENCIA DE LOS GLOBULOS ROJOS

SUMMARIO

Se llevó a cabo una comparación de dos microfiltros a malla de pantalla fina y del equipo de administración de sangre Baxter usado comúnmente en los hospitales del R.U. respecto de sus efectos en la supervivencia de los glóbulos rojos de sangre autóloga almacenada transfundida en seis hombres sanos. El efecto de las transfusiones filtradas sobre el intercambio de gas pulmonar y la coagulación de la sangre fué medido. No hubo ninguna diferencia significativa entre la supervivencia de los glóbulos rojos de transfusión provenientes ya sea de los microfiltros ya sea del equipo Baxter. La transfusión de una unidad de sangre completa no afectó el intercambio de gas pulmonar ni tampoco la coagulación. Las concentraciones post-transfusión de bilirubina fueron significativamente menores con uno de los microfiltros en comparación con el equipo Baxter, posiblemente por causa de la retención de los glóbulos rojos gastados dentro del filtro. Un resultado imprevisto lo constituyó el efecto de la transfusión al aumentar la numeración de neutrófilos en la sangre periférica.

Br. J. Anaesth. (1980), **52**, 305

PLASMA CONCENTRATIONS OF NORADRENALINE AND ADRENALINE AND PLASMA RENIN ACTIVITY DURING EXTRADURAL BLOCKADE IN DOGS

B. STANEK, M. SCHWARZ, M. ZIMPFER AND G. RABERGER

SUMMARY

Anaesthetized dogs (pentobarbitone 25 mg kg^{-1} + 3 mg kg^{-1} h^{-1}) with a Teflon catheter inserted to the femoral artery for pressure and heart rate measurement and blood sampling were studied. Extradural puncture was carried out at L7–S1 under x-ray control and 2% lignocaine (1 ml min^{-1}) infused for approximately 10 min. During extradural block a decrease in arterial pressure was accompanied by a simultaneous decrease in plasma noradrenaline concentration (NA) and a compensatory increase in plasma renin activity (PRA), which became significant 15 min after commencing the block when the arterial pressure was at the minimum. Dihydroergotamine (DHE) led to a rapid reversal of the hypotension with no change in heart rate and a decrease in PRA. Hypovolaemia (blood loss 5 ml kg^{-1}) was induced before and during block, respectively, in two further experimental groups. Increased NA and PRA were found under hypovolaemia without extradural block, but only PRA increased with hypovolaemia and a block. The effects of DHE in the later studies were comparable to those observed in the initial study.

Numerous studies have been performed to assess the response of the autonomic nervous system to anaesthesia and surgery in man (Nikki et al., 1972; Hine et al., 1976; Hirvonen et al., 1978; Nistrup-Madsen et al., 1978; Balogh et al., 1979). Both surgery and anaesthesia can influence the sympathetic nervous system individually. Surgical stress or reflexly mediated increases in sympathetic tone, or both, occur as a result of surgical manipulation to an extent depending on the procedure employed. General anaesthesia can also cause changes in sympathetic tone as reflected by the catecholamine concentrations both in plasma and in urine. Stimulation of sympathetic activity is found with cyclopropane, but with halothane the sympathetic response is depressed (Perry, Van Dyke and Theye, 1974; Roizen et al., 1974; Stokke et al., 1978). Certain anaesthetics, especially volatile halogenated compounds like halothane, sensitize the myocardium to catecholamines, exogenous or endogenous (Katz and Katz, 1966; Katz, 1967; Kehlet, 1978).

The effect of extradural blockade on plasma catecholamine concentrations has not been investigated so far, but it is generally accepted that extradural blockade interferes with the normal function of the sympathetic nervous system (Bonica et al., 1966; Bromage, 1967; Bonica, Berges and Morikawa, 1970; Bonica et al., 1971; Bonica et al., 1972). Blockade of the sympathetic nervous system by extradural blockade may cause a marked decrease in arterial pressure which needs therapeutic compensation. So far, noradrenaline (NA), adrenaline (A) or ephedrine have been the main vasopressor agents used (Smith and Porter, 1915; Ockerblad and Dillon, 1927; Churchill-Davidson, 1951). There is one report of the clinical use of dihydroergotamine (DHE) in treating hypotension (Castenfors, Lindblad and Mortasawi, 1975) which was only recently supported by the experimental findings of Zimpfer and others (1979).

This study was undertaken to answer the following questions: Is there any stimulation of the adrenergic system with increase in plasma catecholamine concentrations during early extradural blockade? Are there any consistent changes in plasma renin activity (PRA) with the onset or following established extradural blockade? To what extent does hypovolaemia influence the effects of extradural blockade and how are the effects of extradural blockade alone or with additional hypovolaemia influenced by DHE, a vasotonic substance?

BRIGITTE STANEK, M.D.; MARTIN SCHWARZ, M.D.; GERHARD RABERGER, M.D.; Pharmakologisches Institut, Universität Wien, Währingerstrasse 13a, A-1090 Wien, Austria. MICHAEL ZIMPFER, M.D.; Univ. Klinik für Anaesthesie und allgemeine Intensivmedizin, Universität Wien, Spitalgasse 23, A-1090 Wien, Austria.
Correspondence to B. S.

0007-0912/80/030305-07 $01.00

© Macmillan Journals Ltd 1980

MATERIALS AND METHODS

Extradural nerve block was induced in 17 mongrel dogs of either sex, mean weight 28.6 ± (SEM) 0.5 kg after anaesthesia had been induced with pentobarbitone 25 mg kg^{-1} + 3 mg kg^{-1} h^{-1} i.v. The trachea was intubated and the dogs breathed spontaneously. A Teflon catheter was inserted percutaneously to the femoral artery for pressure and heart rate measurements and blood sampling for determination of catecholamines and PRA. Extradural puncture was performed at L7–S1 under x-ray control using a thin-wall modified Hustead extradural needle (Abbott Laboratories). A radio-opaque Teflon catheter was advanced through the needle into the extradural space. Blockade was established by constant infusion of lignocaine (Xylocain 2% Astra) via the catheter. The infusion was stopped upon the reversal of the initial increase in heart rate. The mean infusion period was 10.8 ± (SEM) 0.4 min.

Arterial samples (2 ml) for determination of NA and A were collected in chilled ammonium–heparin tubes containing solid reduced glutathione to give a final concentration of 5 mmol $litre^{-1}$. Arterial samples (2 ml) for determination of PRA were collected in similar tubes containing 10% EDTA solution to give a final concentration of 0.1%. Blood was immediately centrifuged at a temperature of 2 °C (3000 *g* for 5 min). Plasma was stored at −35 °C for the determination of catecholamines which was carried out within 2 weeks according to the radioenzymatic method of Da Prada and Zürcher (1976). For PRA, plasma was stored at −20 °C for up to 1 month and determinations were performed by radioimmunoassay according to Haber and others (1969). First samples were taken 1 h after extradural and femoral puncture under pentobarbitone anaesthesia. Two samples were taken with an interval of 5 min, the mean value serving as first control. Three different experimental conditions were fulfilled:

Group 1: *Extradural block, DHE* 30 *min after the start of block* (*n* = 7)

The influence of extradural blockade on arterial pressure, heart rate, NA, A and PRA was investigated by sampling at 2-min intervals for up to 10 min, when the extradural lignocaine infusion was stopped and then at 15, 20 and 30 min after commencement of the infusion. At this time DHE (Dihydergot Sandoz 10 μg kg^{-1} i.v.) was administered and sampling continued at 35, 40 and 50 min, the last value before DHE serving as control for the changes caused by DHE.

Group 2: *Extradural block* 20 *min after induction of hypovolaemia*; *DHE* 30 *min thereafter* (*n* = 5)

The first sample served as control for the effects of moderate hypovolaemia caused by bleeding from the femoral artery (5 ml kg^{-1} within 7.9 ± (SEM) 0.7 min). Further sampling was carried out at 15 and 20 min after the hypovolaemia was established. Extradural block was induced after the 20-min sample. Thereafter the sampling programme was the same as in group 1, as was the administration of DHE.

Group 3: *Hypovolaemia* 30 *min after the start of extradural block, DHE* 20 *min thereafter* (*n* = 5)

Extradural blockade was established after control sampling as in group 1, but samples were taken at 20 min and 30 min only, after the block. At 30 min hypovolaemia was induced as in group 2 (5 ml kg^{-1} within 7.9 ± (SEM) 0.7 min). Sampling occurred at 40, 45 and 50 min after the start of the block—10, 15 and 20 min after induction of hypovolaemia.

At 50 min DHE 10 μg kg^{-1} i.v. was administered. Samples were taken at 60 and 70 min after the start of extradural blockade. The control for the elicited effects of DHE was the last value during hypovolaemia taken 50 min after the start of extradural block.

Statistical evaluation was performed using *t* test for paired data.

RESULTS

The control values for all measurements are given in table I.

TABLE I. *Control values for all measurements* (*mean* ± *SEM*, *n* = 17)

	Mean	SEM
Body weight (kg)	28.6	0.5
Heart rate (beat min^{-1})	135.0	5.3
$P_{art.\ syst}$ (kPa)	23.7	0.66
$P_{art.\ diast}$ (kPa)	13.8	0.54
Noradrenaline concn (pg ml^{-1})	184.0	20.0
Adrenaline concn (pg ml^{-1})	47.0	15.0
Plasma renin activity (ng ml^{-1} h^{-1})	1.99	0.27

Group 1 (figs 1, 2)

Extradural block led to an initial increase in heart rate with a subsequent decrease to less than the initial value. Arterial pressure decreased progressively, reaching the minimum value 15–20 min after the start of the block. NA remained unchanged during the initial period and started to decrease after 6 min, also reaching the minimum at 15–20 min. A did not change significantly over the observation period.

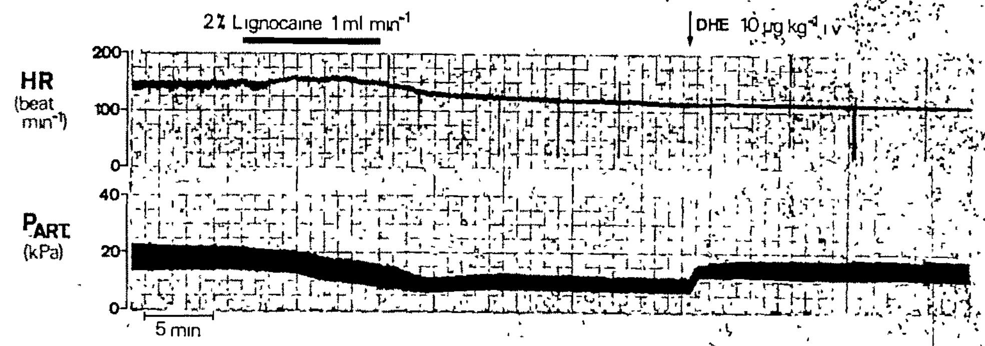


FIG. 1. Original recording. Influence of extradural block and dihydroergotamine injection on arterial pressure and heart rate. Male dog, 29 kg.

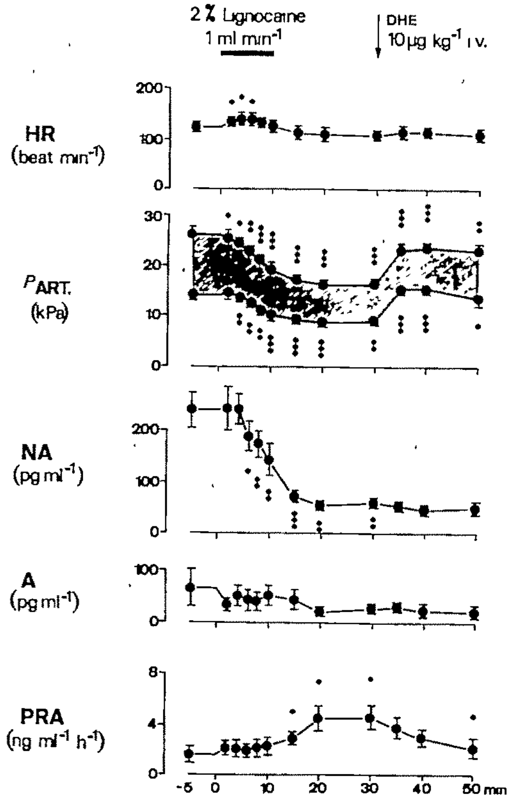


FIG. 2. Group 1: Dihydroergotamine 30 min after the start of extradural block. Mean values ± SEM (seven dogs) of heart rate (HR), arterial pressure ($P_{art.}$), plasma noradrenaline (NA) and adrenaline (A) concentration and plasma renin activity (PRA). Significance: $*0.05 > P > 0.01$; $**0.01 > P > 0.001$; $***P < 0.001$.

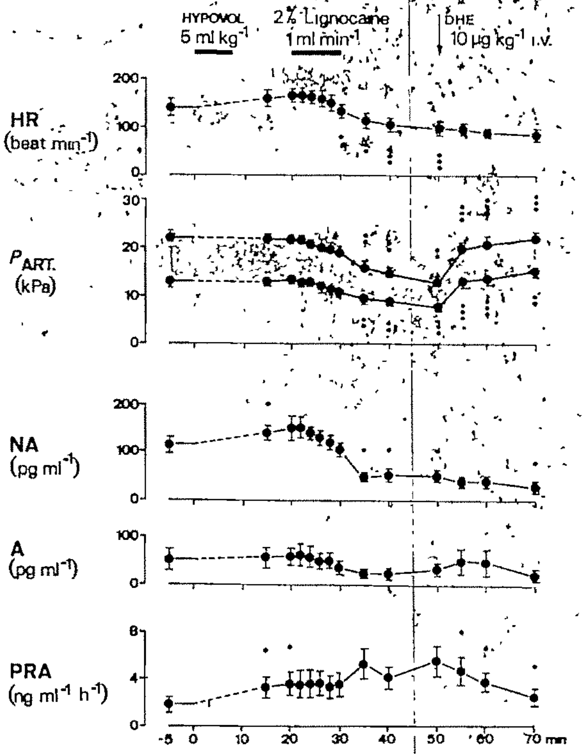


FIG. 3. Group 2: Extradural block 20 min after the start of hypovolaemia, dihydroergotamine 30 min thereafter. Mean values ± SEM (five dogs). For abbreviations and significance symbols see figure 2.

The increase in PRA became statistically significant 15–20 min after the start of the block. DHE, given 30 min after the start of the block, caused a marked increase in arterial pressure and a decrease in PRA. Heart rate, NA and A remained unchanged after the administration of DHE.

Group 2 (fig. 3)

Hypovolaemia before extradural block led to significant increases in NA and PRA and a slight increase in heart rate. Arterial pressure and A remained unaltered. The effects of extradural block 20 min after the start of hypovolaemia and of DHE, led to changes comparable to those observed during extradural block without prior hypovolaemia (group 1).

Group 3 (fig. 4)

Hypovolaemia 30 min after the start of extradural block caused an additional increase in PRA. In contrast to the results with hypovolaemia before extradural block, NA and heart rate were not increased by hypovolaemia during the block. Arterial pressure and A also remained unaltered. DHE led to changes similar to those in groups 1 and 2—an increase in arterial pressure and a decrease in PRA, while the heart rate was unaffected.

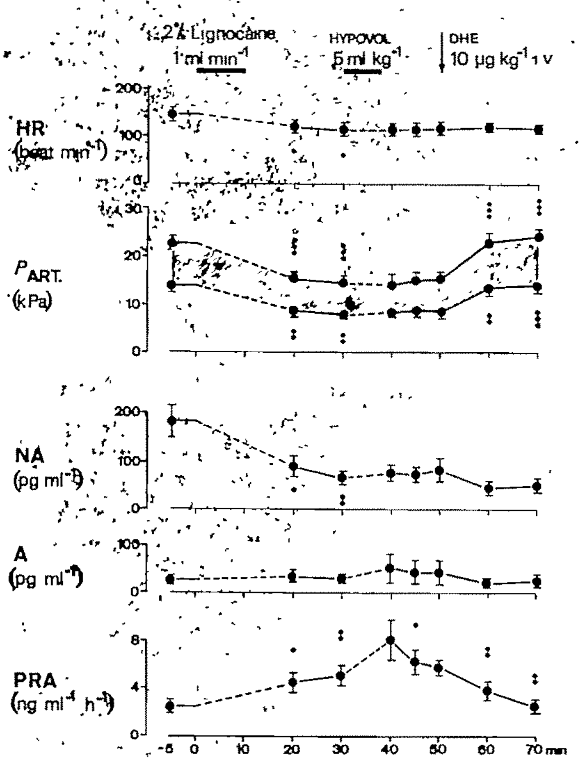


FIG. 4. Group 3: Hypovolaemia 30 min after the start of extradural blockade, dihydroergotamine 20 min thereafter. Mean values ± SEM (five dogs). For abbreviations and significance symbols see figure 2.

DISCUSSION

It is known that extradural block influences the activity of the autonomic afferent and efferent fibres (Bromage, 1967) and plasma concentrations of some hormones (Kehlet, 1978). However, the extent to which blockade of autonomic fibres affects the non-blocked regions or the plasma catecholamine concentration and PRA is unknown. It is likely that blockade of the lower half of the body, with the attendant decrease of the venous return, causes a reflex constrictory response via increased sympathetic tone in the intact regions. This study was designed to assess whether this can be verified by measuring the concentrations of circulating plasma catecholamines.

The decrease in arterial pressure was accompanied during the early phase of regional extradural blockade by an increase in heart rate, suggesting enhanced sympathetic tone, at least with respect to the heart. However, no increase in plasma catecholamine concentrations was found during the early phase of extradural block. This seems to be a result of regional hypofunction in the area of block with a compensatory increase in NA release in unaffected regions. Starting with the 6th min after the commencement of the infusion, NA concentrations were markedly decreased, although the heart rate was still within the range of the control values. The decrease in heart rate which usually occurred between the 8th and 10th min of the infusion can be taken as a sign of high thoracic extradural blockade (McLean et al., 1967), since sympathetic cardiac efferent fibres have their origin above T4 (White, 1957). Heart rate, arterial pressure and plasma NA concentrations reached minimum values 10–20 min after the end of the infusion. The extremely small concentrations of plasma NA indicate that adrenergic neurones in the blocked regions do not contribute further to the NA overflow.

Haemodynamic adjustments are not only a function of the sympathetic system. Recent studies have shown the important role of the renin–angiotensin system in circulatory homeostasis (Davis and Freeman, 1976; Yun, 1979). An increase in renin secretion may originate from a decrease in central venous pressure or a decrease in arterial pressure (Thames, Jarecki and Donald, 1978). A decrease in arterial pressure leads to stimulation of carotid sinus and aortic baroreceptors, irrespective of the starting arterial pressure value, whereas stimulation of the intra-renal baroreceptors (Witty et al., 1972; Tanigawa, Dua and Assaykeen, 1974) occurs only with arterial pressures less than about 75 mm Hg (Abe et al., 1973). In our study a marked increase in PRA was observed 10–20 min after the end of the extradural infusion of lignocaine. This increase seems to be a result of stimulation of the intra-renal baroreceptors. A small increase in PRA during the infusion period, when the arterial pressure was still in the normal range, may be attributable to venous pooling and a reflex increase in PRA caused by stimulation of the low-pressure receptors (Brennan et al., 1971).

Slight haemorrhage led to a compensatory increase in heart rate, plasma NA and PRA. The effects of extradural blockade were unaffected by prior bleeding. A compensatory increase in PRA was also observed, although starting values of PRA before extradural lignocaine infusion were already significantly increased in response to hypovolaemia. PRA also increased significantly when hypovolaemia was induced during extradural block, although the baseline values were significantly greater in comparison with values before blockade. In contrast to hypovolaemia before extradural block, sympathetic counter-regulation, as judged from changes in heart rate and plasma NA, did not occur if hypovolaemia was induced during extradural block.

These results indicate that PRA plays a major role in arterial pressure regulation during extradural block, at the time when the sympathetic nervous system cannot react to stimuli. NA concentrations remained constantly small under hypovolaemia under extradural blockade, whereas an increase in plasma A was observed in conjunction with the marked increases in PRA in three of five experiments in group 3 (hypovolaemia + extradural block). This secretion of A must be independent of the integrity of the innervation of the adrenal medulla, since extradural block was still fully effective during this period. It can be assumed that the large increase in PRA is the cause for A release, since recent studies suggest that angiotensin stimulates the innervated and isolated perfused adrenal medulla (Peach, 1971; Ackerly, Sarstedt and Peach, 1977; Feuerstein and Cohen, 1979).

As extradural block quite often leads to marked decreases in arterial pressure in clinical practice, it was of interest to study further the effects of a vasotonic substance on the haemodynamic and biochemical changes of extradural block with or without additional hypovolaemia. DHE seemed to be an appropriate substance since it is known to increase the arterial pressure by mobilization of blood from the capacitance vessels and also by restoring arterial resistance to normal. In contrast to catecholamines, DHE is devoid of a positive chronotropic action; indeed it may cause a decrease in heart rate, as shown recently in intact anaesthetized dogs (Raberger, Benke and Schwarz, 1979). As anticipated, DHE led to an improvement of the arterial pressure during extradural block without change in heart rate. This could be assumed to render vasotonic circulatory counter-regulation unnecessary. Indeed, PRA values were found to decrease consistently after the administration of DHE. The plasma half-life of PRA calculated from the data of all groups was in the region of 16 min according to the equation:

$$\log \mathrm{PRA} = 0.677718 - 0.0187887\ \mathrm{min}\ (n = 63,\ P < 0.001).$$

The results presented show that endogenous circulatory regulation is not sufficient to prevent the marked decrease in arterial pressure during high extradural blockade. In our study the adrenergic system did not participate in this regulation by the sympathetic activation of noradrenergic neurones as seen from the plasma NA concentrations, nor by the secretion of A and NA from the adrenal medulla as shown by the plasma A concentrations. The only adjustment which was found in our study was a marked increase in PRA. Unfortunately, plasma vasopressin concentrations were not determined and thus the participation of vasopressin cannot be quantitatively evaluated. It must, however, be assumed that vasopressin, which is known to be rapidly released in response to adequate stimuli (Share, 1968), should also be found to be increased, since afferent impulses should not be blocked in the experimental procedure described above.

Irrespective of the release of vasotonic peptides, the aspect of clinical importance is the still notable decrease in arterial pressure. This decrease can be counteracted pharmacologically by vasotonic agents. DHE appears to be a favourable drug, since restoration of the arterial pressure can be achieved without any increase in heart rate and, hence, without additional oxygen requirement by the heart.

ACKNOWLEDGEMENTS

We are grateful to Dr L. Kastner for correction of the English text and to Mrs E. Kotai for expert technical assistance.

REFERENCES

Abe, Y., Okahara, T., Kishimoto, T., Yamamoto, K., and Ueda, J. (1973). Relationship between intrarenal distribution of blood flow and renin secretion. *Am. J. Physiol.*, **225**, 319.

Ackerly, J. A., Sarstedt, C. A., and Peach, M. J. (1977). Peptide antagonists of angiotensin-induced adrenal catecholamine release. *Eur. J. Pharmacol.*, **42,** 391.

Balogh, D., Hammerle, A. F., Hortnagl, H., Brücke, T., and Stadler-Wollfersgrun, R. (1979). Plasma-Katecholamine bei Halothan-N_2O-Anaesthesie und Neuroleptanalgesie: Intra- und Postoperative Vergleichsstudie. *Anaesthesist*, **28,** 517.

Bonica, J. J., Akamatsu, T. J., Berges, P. U., Morikawa, K. and Kennedy, W. F. jr. (1971). Circulatory effects of peridural block. II: Effects of epinephrine. *Anesthesiology*, **34,** 514.

—— Berges, P. U., and Morikawa, K. (1970). Circulatory effects of peridural block. I: Effects of level of analgesia and dose of lidocaine. *Anesthesiology*, **33,** 619.

—— Kennedy, W. F. jr, Akamatsu, T. J., and Gerbershagen, H. U. (1972). Circulatory effects of peridural blocks. III: Effects of acute blood loss. *Anesthesiology*, **36,** 219.

—— Ward, R. J., and Tolas, A. G. (1966). A comparison of the effects of high subarachnoid and epidural anaesthesia. *Acta Anaesthesiol. Scand.*, (Suppl.), **23,** 429.

Brennan, L. A. jr, Malvin, R. L., Jochim, K. E., and Roberts, D. E. (1971). Influence of right and left atrial receptors on plasma concentrations of ADH and renin. *Am. J. Physiol.*, **221,** 273.

Bromage, P. R. (1967). Physiology and pharmacology of epidural analgesia. A review. *Anesthesiology*, **28,** 592.

Castenfors, J., Lindblad, L. E., and Mortasawi, A. (1975). Effect of dihydroergotamine on peripheral circulation during epidural anaesthesia in man. *Acta Anaesthesiol. Scand.*, **19,** 79.

Churchill-Davidson, H. C. (1951). L-Noradrenaline as a vasoconstrictor. *Br. Med. J.*, **12,** 1551.

Da Prada, M., and Zürcher, G. (1976). Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range. *Life Sci.*, **19,** 1161.

Davis, J. O., and Freeman, R. H. (1976). Mechanisms regulating renin release. *Physiol. Rev.*, **56,** 1.

Feuerstein, G., and Cohen, S. (1979). Modification by SQ 14225 of blood pressure and adrenal catecholamine response to hemorrhage. *Eur. J. Pharmacol.*, **55,** 203.

Haber, E., Korner, T., Page, L. B., Kliman, B., and Purnode, A. (1969). Application of a radioimmunoassay for angiotensin I to the physiologic measurement of plasma renin activity in normal human subjects. *J. Clin. Endocrinol. Metab.*, **29,** 1349.

Hine, I. P., Wood, W. G., Mainwaring-Burton, R. W., Butler, M. J., Irving, M. H., and Booker, B. (1976). The adrenergic response to surgery involving cardiopulmonary bypass, as measured by plasma and urinary catecholamine concentrations. *Br. J. Anaesth.*, **48,** 355.

Hirvonen, J., Huttunen, P., Nuutinen, L., and Pekkarinen, A. (1978). Catecholamines and free fatty acids in plasma of patients undergoing cardiac operations with hypothermia and bypass. *J. Clin. Pathol.*, **31,** 949.

Katz, R. L., (1967). Clinical experience with neurogenic cardiac arrhythmias. *Bull. N.Y. Acad. Med.*, **43,** 1106.

—— Katz, G. J. (1966). Surgical infiltration of pressor drugs and their interaction with volatile anaesthetics. *Br. J. Anaesth.*, **38,** 712.

Kehlet, H. (1978). Influence of epidural analgesia on the endocrine-metabolic response to surgery. *Acta Anaesthesiol. Scand.* (Suppl.), **70,** 39.

McLean, A. P. H., Mulligan, G. W., Otton, P., and MacLean, L. D. (1967). Hemodynamic alterations associated with epidural anesthesia. *Surgery*, **62,** 79.

Nikki, P., Takki, S., Tammisto, T., and Jäättelä, A. (1972). Effect of operative stress on plasma catecholamine levels. *Ann. Clin. Res.*, **4,** 146.

Nistrup-Madsen, S., Fog-Moller, F., Christiansen, C., Vester-Andersen, T., and Enquist, A. (1978). Cyclic AMP, adrenaline and noradrenaline in plasma during surgery. *Br. J. Surg.*, **65,** 191.

Ockerblad, N. F., and Dillon, T. G. (1927). The use of ephedrine in spinal anesthesia; preliminary report. *J.A.M.A.*, **88,** 1135.

Peach, M. J. (1971). Adrenal medullary stimulation induced by angiotensin I, angiotensin II, and analogues. *Circ. Res.* (Suppl. II), **28–29,** 107.

Perry, L. B., Van Dyke, R. A., and Theye, R. A. (1974). Sympathoadrenal and hemodynamic effects of isoflurane, halothane and cyclopropane in dogs. *Anesthesiology*, **40,** 465.

Raberger, G., Benke, Th., and Schwarz, M. (1979). Effects of dihydroergotamine (DHE) on pulmonary and systemic circulation. *Proc. Internatl Symp. Pulmonary Circulation III*, Prague.

Roizen, M. F., Moss, J., Henry, D. P., and Kopin, I. J. (1974). Effects of halothane on plasma catecholamines. *Anesthesiology*, **41,** 342.

Share, L. (1968). Control of plasma ADH titer in hemorrhage: role of atrial and arterial receptors. *Am. J. Physiol.*, **215,** 1384.

Smith, G. G., and Porter, W. T. (1915): Spinal anesthesia in the cat. *Am. J. Physiol.*, **38,** 108.

Stokke, D. B., Christensen, N. J., Hole, P., Andersen, P. K., and Juhl, B. (1978). Plasma catecholamines during equipotent anaesthesia with cyclopropane and halothane–N_2O in man. *Anaesthesist*, **27,** 469.

Tanigawa, H., Dua, S. L., and Assaykeen, T. A. (1974). Effect of renal and adrenal denervation on the renin response to slow haemorrhage in dogs. *Clin. Exp. Pharmacol. Physiol.*, **1,** 325.

Thames, M. D., Jarecki, M., and Donald, D. E. (1978). Neural control of renin secretion in anesthetized dogs. Interaction of cardiopulmonary and carotid baroreceptors. *Circ. Res.*, **42,** 237.

White, J. C. (1957). Cardiac pain. Anatomic pathways and physiologic mechanisms. *Circulation*, **16,** 644.

Witty, R. T., Davis, J. O., Shade, R. E., Johnson, J. A. and Prewitt, R. L. (1972). Mechanisms regulating renin release in dogs with thoracic caval constriction. *Circ. Res.*, **31,** 339.

Yun, J. C. H. (1979). On the control of renin release. *Nephron*, **23,** 72.

Zimpfer, M., Raberger, G., Schwarz, M., and Stanek, B. (1979). Changes in limb circulation under dihydroergotamine (DHE) in peridural anaesthesia. *Proc. Internatl Symp. Hemodynamics of the Limb*, Toulouse.

CONCENTRATIONS DE NORADRENALINE ET D'ADRENALINE DANS LE PLASMA ET ACTIVITE RENINE DU PLASMA PENDANT UN BLOCAGE EXTRADURAL CHEZ LES CHIENS

RESUME

On a observé des chiens anesthésiés (à l'aide de pentobarbitone à raison de 25 mg $kg^{-1}+3$ mg kg^{-1} h^{-1}) auxquels on avait inséré un cathéter en Téflon dans l'artère fémorale afin de mesurer la fréquence et la pression cardiaque et de procéder à un échantillonnage du sang. La ponction extradurale a été faite entre L7–S1 sous contrôle radiographique et on a infusé de la lignocaîne à 2% (1 ml min^{-1}) pendant environ 10 min. Pendant le blocage extradural, la diminution de la pression artérielle a été accompagnée d'une diminution simultanée des concentrations de noradrénaline dans le plasma (NA) et d'une augmentation compensatoire de l'activité rénine de plasma (PRA), qui est devenue significative 15 min après le commencement du blocage, alors que la pression artérielle était à son minimum. La dihydroergotamine (DHE) a entraîné une inversion rapide de l'hypotension, sans qu'il y ait de changement dans la fréquence cardiaque, mais il y a eu une diminution de la PRA. On a provoqué avant et pendant le blocage une hypovolémie (perte de sang de 5 ml kg^{-1}) sur deux autres groupes expérimentaux. On a constaté une augmentation de la NA et de la PRA sous hypovolémie sans blocage extradural, mais seule la PRA a augmenté avec l'hypovolémie et le blocage. Les effets de DHE dans ces dernières études ont été comparables à ceux observés au cours de l'étude initiale.

PLASMAKONZENTRATIONEN VON ADRENALIN UND NORADRENALIN, UND PLASMARENINAKTIVITÄT BEI EXTRADURALER BLOCKIERUNG BEI HUNDEN

ZUSAMMENFASSUNG

Narkotisierte Hunde (Pentobarbiton 25 mg $kg^{-1}+3$ mg kg^{-1} h^{-1}) mit einem Teflon-Katheter in der Femuralarterie zur Messung von Druck und Herztätigkeit sowie zur Entnahme von Blutproben wurden studiert. Extradurale Punktierung wurde bei L7–S1 unter Röntgenkontrolle durchgefuhrt, und 10 Minuten lang wurden 2% Lignocain (1 ml min^{-1}) verabreicht. Wahrend der extraduralen Blockierung sank der arterielle Druck bei gleichzeitigem Absinken der Plasmanoradrenalinkonzentration (NA) und ausgleichendem Anstieg der Plasmareninaktivität (PRA), die 15 min nach Beginn der Blockierung bei minimalem arteriellem Druck deutlich wurde. Dihydroergotamin (DHE) führte zu schneller Umkehrung der Hypotension ohne Veränderung der Herztätigkeit und bei sinkendem PRA. Hypovolämie (Blutverlust 5 ml kg^{-1}) wurde in 2 weiteren experimentellen Gruppen eingeleitet Erhohte NA und PRA gab es bei Hypovolämie ohne Blockierung, doch bei Hypovolämie mit Blockierung stieg nur PRA an. Wirkungen von DHE in späteren Studien waren vergleichbar mit den in der ersten Studie beobachteten.

CONCENTRACIONES EN EL PLASMA DE NORADRENALINA Y ADRENALINA Y ACTIVIDAD RENAL PLASMATICA DURANTE EL BLOQUEO EXTRADURAL EN PERROS

SUMARIO

Se llevó a cabo el estudio de perros anestesiados (pentobarbitona 25 mg $kg^{-1}+3$ mg kg^{-1} h^{-1}) con sonda de Teflón insertada en la arteria femoral con miras a medir la presión y el ritmo cárdiacos así como a tomar muestras de sangre. Se realizó la punción en L7–S1 bajo control radiográfico y se infusó lignocaina al 2% (1 ml min^{-1}) durante approximadamente 10 min. Durante el bloqueo extradural, una disminución de la presión arterial se acompañó de un descenso simultáneo de la concentración de noradrenalina en el plasma (NA) y de un aumento compensatorio de la actividad renal plasmática (ARP), que se volvió significativa 15 min después del comienzo del bloqueo cuando la presión arterial se encontraba en su mínimo. La dihidroergotamina (DHE) llevó a una rápida inversión de la hipotensión sin cambio alguno en el ritmo cárdiaco y una disminución del ARP. Se indujo una hipovolemia antes y durante el bloqueo (pérdida de sangre 5 ml kg^{-1}), respectivamente, en dos grupos experimentales adicionales. Se observó NA y ARP en aumento bajo hipovolemia sin bloqueo extradural, pero sólo el ARP aumentó con hipovolemia y un bloqueo. Los efectos de la DHE en estudios ulteriores fueron comparables con los anotados en el estudio inicial.

Br. J. Anaesth. (1980), **52**, 313

INHIBITION OF NEURONAL UPTAKE OF NORADRENALINE IN THE ISOLATED PERFUSED RAT HEART BY PANCURONIUM AND ITS HOMOLOGUES, ORG. 6368, ORG. 7268 AND NC45

P. J. Salt, P. K. Barnes and C. M. Conway

SUMMARY

The cardiovascular effects of pancuronium may be caused partly by an interaction of this drug with the sympathetic nervous system. We examined one possible mechanism of interaction, the effect on the re-uptake processes for noradrenaline. Pancuronium and its closely related steroidal homologues, Org. 6368, Org. 7268 and NC 45, were studied at a high concentration (500 μmol litre^{-1}) for inhibition of the uptake of tritiated noradrenaline into neuronal sites (Uptake$_1$) and extraneuronal sites (Uptake$_2$) in the isolated perfused rat heart. All drugs tested caused almost total inhibition of Uptake$_1$. The bis-quaternary steroids pancuronium and Org. 6368 were selective for Uptake$_1$ inhibition, the mono-quaternary steroids Org. 7268 and NC45 also produced significant inhibition of Uptake$_2$. Uptake$_1$ inhibition was investigated in detail using lesser concentrations of the compounds. All four steroids were found to cause a concentration-dependent inhibition of Uptake$_1$. It seems likely, therefore, that inhibition of neuronal uptake of noradrenaline plays a significant role in the aetiology of the chronotropic actions of pancuronium in the rat.

Pancuronium bromide is a bis-quaternary steroid, which is a potent non-depolarizing antagonist of neuromuscular transmission (Buckett, Hewett and Savage, 1967). It possesses minimal ganglion-blocking and histamine-releasing properties (Buckett et al., 1968) and does not produce the hypotension seen with tubocurarine (Loh, 1970; Smith, Proctor and Spence, 1970; Nightingale and Bush, 1973).

Pancuronium can affect the cardiovascular system by several mechanisms. Vagolytic properties of pancuronium have been demonstrated in the cat (Hughes and Chapple, 1976), the dog and the guinea-pig (Saxena and Bonta, 1970). It can affect the uptake mechanisms for noradrenaline in the rat. This has been shown directly in the isolated perfused rat heart (Ivankovich et al., 1975), indirectly in the pithed rat (Docherty and McGrath, 1978), and in the isolated rat vas deferens (Quintana, 1977). Pancuronium also produces indirect sympathetic stimulation in the dog (Domenech et al., 1976).

This study was designed to investigate in detail the effect of pancuronium in the isolated perfused rat heart on the uptake of tritiated noradrenaline into neuronal sites, a process termed Uptake$_1$ (Iversen, 1963), and to look for possible inhibition of extraneuronal uptake of tritiated noradrenaline which has been designated Uptake$_2$ (Iversen, 1965). The effects produced by pancuronium were compared with those produced by its steroidal neuromuscular blocking homologues, NC 45, Org. 6368 and Org. 7268.

MATERIALS AND METHODS

Male albino Wistar rats weighing 150–250 g were killed by cervical dislocation and their hearts were removed and perfused by the Langendorff technique as previously described (Iversen, 1963). The perfusion medium was a Krebs–Henseleit solution to which was added EDTA disodium salt at a concentration of 10 mg litre^{-1} and ascorbic acid 20 mg litre^{-1} to reduce auto-oxidation of noradrenaline and glucose 1 g litre^{-1}. The Krebs solution was gassed with 5% carbon dioxide in oxygen and maintained at 37 °C. After perfusion for 1 min with amine-free solution the hearts were perfused with Krebs solution containing tritiated DL-noradrenaline (The Radiochemical Centre Amersham 13.0 Ci mmol^{-1}) diluted with non-radioactive DL-noradrenaline to a final concentration of 10 ng ml^{-1} and 50 nCi ml^{-1} for Uptake$_1$ experiments and 5 μg ml^{-1} and 125 nCi ml^{-1} for Uptake$_2$ experiments (Iversen, Salt and Wilson, 1972). All drugs tested were dissolved directly in this Krebs solution containing tritiated

---

P. J. Salt,* M.B., B.CHIR., PH.D., Department of Clinical Measurement; P. K. Barnes, M.B., B.S., F.F.A.R.C.S.; C. M. Conway, M.B., B.S., F.F.A.R.C.S., Magill Department of Anaesthetics, Westminster Hospital, London.

* Present address: Department of Anaesthetics, Bristol Royal Infirmary, Bristol BS2 8HW.

Correspondence to P. K. B.

0007–0912/80/030313–05 $01.00

© Macmillan Journals Ltd 1980

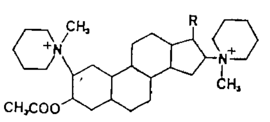
DL-noradrenaline immediately before each experiment. The four drugs investigated were initially tested for inhibition of $Uptake_1$ and $Uptake_2$ at concentrations of 500 μmol $litre^{-1}$. Subsequently, dose–response curves for $Uptake_1$ inhibition by the four compounds were obtained by using a range of drug concentrations because of the selectivity of action of pancuronium for $Uptake_1$. For $Uptake_1$ screening perfusion was continued with tritiated DL-noradrenaline for 10 min and in the case of $Uptake_2$ for 4 min. The hearts were then removed, blotted free of perfusion medium and homogenized in 1% EDTA 2 ml; 10 ml of acid ethanol was then added and the samples centrifuged at 3000 rev min^{-1} for 10 min. The radioactivity in 1-ml aliquots of the supernatant was measured in a Packard Tri-Carb liquid scintillation spectrometer after adding Biofluor 15 ml (New England Nuclear) as scintillator. The tissue content of labelled noradrenaline plus metabolites was calculated after correcting for the presence of tritiated noradrenaline in the extracellular space and, in the case of $Uptake_2$, for the uptake of tritiated noradrenaline into sympathetic nerve terminals (Iversen and Salt, 1970). At each drug concentration six hearts were perfused. A log-probit plot of the results for $Uptake_1$ and $Uptake_2$ was made, and the line of best fit was obtained by the method of least squares. From these plots the concentration of drug producing 50% inhibition of each uptake process (IC_{50}) was calculated.

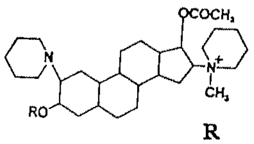
RESULTS

At a concentration of 500 μmol $litre^{-1}$, all four compounds produced almost complete inhibition of $Uptake_1$. Pancuronium appeared to be relatively selective for inhibition of $Uptake_1$. The monoquaternary steroids (Org. 7268 and NC 45, produced considerable inhibition of $Uptake_2$ (table I).

TABLE I. *Inhibition of $Uptake_1$ and $Uptake_2$ by pancuronium and its homologues*

	% inhibition $Uptake_1$ (± SEM) (drug concn 500 μmol $litre^{-1}$)	% inhibition $Uptake_2$ (± SEM) (drug concn 500 μmol $litre^{-1}$)
Pancuronium	94.1 ± 0.6	20.9 ± 8.3
Organon 6368	85.5 ± 0.7	37.4 ± 4.3
Organon NC 45	85.6 ± 0.6	57.0 ± 2.1
Organon 7268	74.9 ± 1.3	86.8 ± 1.4





	R		R
Pancuronium	$OCOCH_3$	Organon NC 45	CH_3CO
Organon 6368	H	Organon 7268	H

When tested at smaller concentrations the compounds produced a dose-dependent inhibition of $Uptake_1$ (fig. 1). Pancuronium was the most potent in this respect with IC_{50} value (concentration of drug producing 50% inhibition of Uptake) of 16.1 μmol $litre^{-1}$; Org. 6368 was 2.4 times less potent than pancuronium, and the corresponding values for

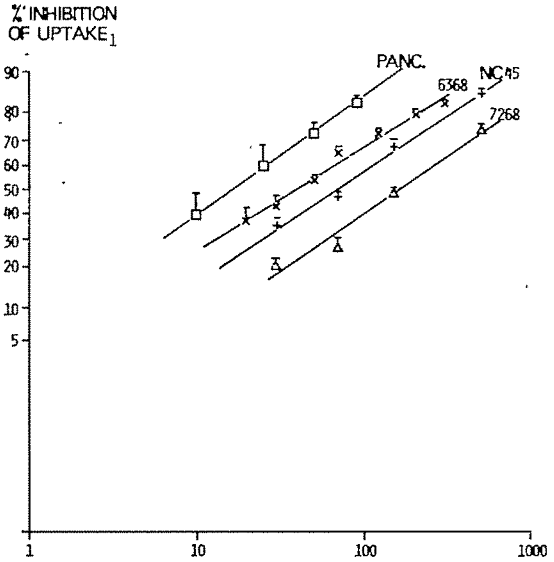


FIG. 1. Inhibition of $Uptake_1$ by pancuronium and its homologues. Percentage inhibition of tritiated noradrenaline (probability scale) is plotted against log concentration of pancuronium (PANC.), Org. 6368, NC 45 and Org. 7268; line fitted by the method of least squares analysis. Each point is the mean value for six hearts; SEM indicated by vertical lines. Uptake of tritiated nor-adrenaline in control hearts was 131 ± 4.7 ng g^{-1} per 10 min (mean ± SEM for 24 hearts).

TABLE II. *IC_{50} values for $Uptake_1$ inhibition. The IC_{50} values and slopes were determined from the graphical data illustrated in figure* 1

	IC_{50} (μmol $litre^{-1}$)	Gradient of dose response curve (probit–log units)
Pancuronium	16.1	1.31
Organon 6368	38.8	1.20
Organon NC 45	67.6	1.24
Organon 7268	158.8	1.27

NC 45 and Org. 7268 were 4.2 and 9.9 respectively (table II).

DISCUSSION

The actions of pancuronium on the cardiovascular system are complex and have been the subject of controversy. In the original evaluation of pancuronium in clinical practice (Baird and Reid, 1967) little effect was noted on arterial pressure and heart rate, and these findings were subsequently confirmed (McDowell and Clarke, 1969). Loh (1970), however, showed that pancuronium produced a significant transient increase in arterial pressure in patients undergoing cardiac surgery. This was confirmed by Kelman and Kennedy (1971), who also documented an increase in heart rate and cardiac output in patients undergoing general surgery. Nightingale and Bush (1973) obtained similar findings in children.

The cause of the cardiovascular side-effects appears to be complicated and multifactorial. Evidence for a vagolytic effect which might explain the tachycardia associated with pancuronium is well established from animal studies (Saxena and Bonta, 1970; Hughes and Chapple, 1976). Nana, Cordan and Domokos (1973) demonstrated an increase in plasma catecholamine concentrations, especially noradrenaline, after injection of pancuronium in man, and there is strong evidence for an interaction between pancuronium and the sympathetic nervous system in animal studies. Ivankovich and his co-workers (1975) showed that pancuronium inhibits uptake of noradrenaline to the isolated perfused rat heart, although their data do not distinguish between inhibition of Uptake$_1$ and Uptake$_2$. These workers used a concentration of noradrenaline (200 ng ml^{-1}) which has been found to saturate Uptake$_1$ and with which Uptake$_2$ accounts for a significant proportion of the observed uptake (Iversen, 1971). In our experiments Uptake$_1$ inhibition was examined using a concentration of noradrenaline in perfusate (10 ng ml^{-1}) at which Uptake$_1$ was the predominant inactivation process for the sympathetic transmitter. In screening for Uptake$_2$ inhibition, a large concentration of noradrenaline (5 μg ml^{-1}) was used. At this concentration Uptake$_1$ is saturated and Uptake$_2$ is the predominant process for the uptake of noradrenaline. Steroids have been shown to be potent and selective inhibitors of Uptake$_2$ (Salt, 1972) and in any examination of the effect of pancuronium on the uptake of noradrenaline, this should be excluded. The processes by which noradrenaline is inactivated *in vivo* and the physiological effects of inhibition of the inactivation processes have been described previously (Salt, Barnes and Beswick, 1979). The results of the present study are in agreement with those of Ivankovich and others (1975). Our study shows that pancuronium is a selective inhibitor of Uptake$_1$ and, despite its steroid nucleus, has a poor affinity for Uptake$_2$ sites. The inhibition of Uptake$_1$ is dose-dependent and the IC$_{50}$ value (16.1 μmol litre^{-1}), determined from our dose–response curve, is of the same order of magnitude as that deduced from the data produced by Ivankovich and others (1975).

This study also confirms the work of Docherty and McGrath (1978), who found indirect evidence that pancuronium is an Uptake$_1$ blocker in the pithed rat. These workers found no potentiation of the chronotropic response to isoprenaline, which is the substrate of choice for Uptake$_2$ and is not transported into Uptake$_1$ sites (Callingham and Burgen, 1966).

Domenech and co-workers (1976), in experiments on dogs, obtained evidence that pancuronium may act indirectly by releasing noradrenaline from sympathetic nerve terminals. However, using the same preparation as ourselves (the isolated perfused rat heart), Ivankovich and others (1975) found no evidence for the release of noradrenaline from sympathetic nerve terminals by pancuronium. Quintana (1977), using the isolated rat vas deferens preparation, was able to show that pancuronium is devoid of indirect adrenergic activity, but he demonstrated an increased sensitivity in the preparation to noradrenaline explicable on the basis of uptake inhibition of the neurotransmitter by pancuronium. It is feasible that pancuronium acts on the sympathetic nerve terminals both by an indirect, tyramine-like mechanism, as well as by inhibition of Uptake$_1$. Species difference may explain the apparent discrepancy in these findings.

The other bis-quaternary steroid tested, Org. 6368, also produced dose-dependent inhibition of Uptake$_1$, although it was less active in this respect than pancuronium. The mono-quartenary steroids tested, NC 45 and Org. 7268, inhibited Uptake$_1$ in a dose-dependent fashion, but to a lesser extent than did the bis-quaternary steroids.

In the screening experiments, at high concentration, the mono-quaternary compounds produced significant inhibition of Uptake$_2$. There appeared to be an inverse relationship between the degree of blockade of Uptake$_1$ and Uptake$_2$ produced by the four drugs tested. Thus, the least active inhibitor of Uptake$_1$, Org. 7268, produced the greatest inhibition of Uptake_2. The structure–activity relationship for inhibition of the two uptake processes may depend, therefore, on the number of charged groups attached to the steroid nucleus. This is in agreement with the findings of Salt (1972) that a wide range of biologically active uncharged steroids were selective for Uptake_2 inhibition and did not inhibit Uptake_1.

Of the compounds examined in this experiment pancuronium is established in clinical practice and NC 45 is undergoing clinical trials. Org. 6368 and Org. 7268 are not at present in clinical use and were included to see how homologues of pancuronium and NC 45 behaved. Pancuronium causes cardiac stimulation in the rat and this paper suggests this may in part be caused by inhibition of Uptake_1. The rat is resistant to the effect of pancuronium at the neuromuscular junction (Sugrue, Duff and McIndewar, 1975). In order to produce prolonged blockade of skeletal muscle twitching in the pithed rat, at least $1\ \text{mg kg}^{-1}$ must be administered (Docherty and McGrath, 1978). The concentration of pancuronium that produced 50% inhibition of Uptake_1 was $11.8\ \mu\text{g ml}^{-1}$. NC 45 is slightly less potent as a neuromuscular blocker in the cat than is pancuronium, and possesses a much wider margin between neuromuscular blocking doses and the doses which produce an increase in heart rate (Durant, 1978). Docherty and McGrath (1979) have shown in the pithed rat that NC 45 is 2.1 times less potent as a relaxant and 33 times less potent as a potentiator of cardiac sympathetic transmission. The concentration of NC 45 that produced 50% inhibition of Uptake_1 was $43.1\ \mu\text{g ml}^{-1}$, nearly four times the IC_{50} of pancuronium. This offers an explanation of why NC 45 appears to be free of cardiovascular side-effects.

ACKNOWLEDGEMENTS

The authors wish to thank Mr R. Tennant for his expert technical assistance and Mrs B. R. Lister for her secretarial skills. The project was supported by grants from the Westminster Hospital Special Trustees and from the North West Thames Regional Research Committee.

REFERENCES

Baird, W. L. M., and Reid, A. M. (1967). The neuromuscular blocking properties of a new steroid compound, pancuronium bromide—a pilot study in man. *Br. J. Anaesth.*, **39**, 775.

Buckett, W. R., Hewett, C. L., and Savage, D. S. (1967). Potent steroidal neuromuscular blocking agents. *Chim. Ther.*, **2**, 186.

—— Marjoribanks, C. E. B., Marwick, F. A., and Morton, M. B. (1968). The pharmacology of pancuronium bromide (Org. NA 97), a new potent steroidal neuromuscular blocking agent. *Br. J. Pharmacol. Chemother.*, **32**, 671.

Callingham, B. A., and Burgen, A. S. V. (1966). The uptake of isoprenaline and noradrenaline by the perfused rat heart. *Molec. Pharmacol.*, **2**, 37.

Docherty, J. R., and McGrath, J. C. (1978). Sympathomimetic effects of pancuronium bromide on the cardiovascular system of the pithed rat: a comparison with effects of drugs blocking the neuronal uptake of noradrenaline. *Br. J. Pharmacol.*, **64**, 589.

—— —— (1979). A comparison of the relaxant and autonomic effects of pancuronium and its monoquaternary derivative, Organon NC 45, in the pithed rat. *Proc. Br. Pharmacol. Soc.*, p. 56.

Domenech, J. S., Garcia, R. S., Rodriguez Sasiain, J. M., Quintana Loyola, A., and Santafé Oroz, J. (1976). Pancuronium bromide: an indirect sympathomimetic agent. *Br. J. Anaesth.*, **48**, 1143.

Durant, N. N. (1978). A comparison in the anaesthetised cat and monkey of pancuronium with a monoquaternary analogue. *Proc. V Eur. Congr. Anaesthesiol. Excerpta Medica no.* 452.

Hughes, R., and Chapple, D. J. (1976). Effects of non-depolarizing neuromuscular blocking agents on peripheral autonomic mechanisms in cats. *Br. J. Anaesth.*, **48**, 59.

Ivankovich, A. D., Miletich, D. J., Albrecht, R. F., and Zahed, B. (1975). The effect of pancuronium on myocardial contraction and catecholamine metabolism. *J. Pharm. Pharmacol.*, **27**, 837.

Iversen, L. L. (1963). The uptake of noradrenaline by the isolated perfused rat heart. *Br. J. Pharmacol.*, **21**, 532.

—— (1965). The uptake of catecholamines at high perfusion concentrations in the rat isolated heart: a novel catecholamine uptake process. *Br. J. Pharmacol.*, **25**, 18.

—— (1971). Third Gaddum Memorial Lecture: Role of transmitter uptake mechanisms in synaptic neurotransmission. *Br. J. Pharmacol.*, **41**, 571.

—— Salt, P. J. (1970). Inhibition of catecholamine Uptake_2 by steroids in the isolated rat heart. *Br. J. Pharmacol.*, **40**, 528.

—— —— Wilson, H. A. (1972). Inhibition of catecholamine uptake in the isolated rat heart by haloalkylamines related to phenoxybenzamine. *Br. J. Pharmacol.*, **46**, 647.

Kelman, G. R., and Kennedy, B. R. (1971). Cardiovascular effects of pancuronium in man. *Br. J. Anaesth.*, **43**, 335.

Loh, L. (1970). The cardiovascular effects of pancuronium bromide. *Anaesthesia*, **25**, 356.

McDowell, S. A., and Clarke, R. S. J. (1969). A clinical comparison of pancuronium with d-tubocurarine. *Anaesthesia*, **24**, 581.

Nana, A., Cordan, E., and Domokos, M. (1973). Blood catecholamine changes after pancuronium. *Acta Anaesthesiol. Scand.*, **17**, 83.

Nightingale, D. A., and Bush, G. H. (1973). A clinical comparison between tubocurarine and pancuronium in children. *Br. J. Anaesth.*, **45**, 63.

Quintana, A. (1977). Effect of pancuronium bromide on the adrenergic reactivity of the isolated rat vas deferens. *Eur. J. Pharmacol.*, **46**, 276.

Salt, P. J. (1972). Inhibition of noradrenaline Uptake_2 in the isolated rat heart by steroids, clonidine and methoxylated phenylethylamines. *Eur. J. Pharmacol.*, **20**, 329.

Salt, P. J., Barnes, P. K., and Beswick, F. J. (1979). Inhibition of neuronal and extra-neuronal uptake of noradrenaline by ketamine in the isolated perfused rat heart. *Br. J. Anaesth.*, **51**, 835.

Saxena, P. R., and Bonta, I. L. (1970). Mechanism of selective cardiac vagolytic action of pancuronium bromide. Specific blockade of muscarinic receptors. *Eur. J. Pharmacol.*, **11**, 332.

Smith, G., Proctor, G. W., and Spence, A. A. (1970). A comparison of some cardiovascular effects of tubocurarine and pancuronium in dogs. *Br. J. Anaesth.*, **42**, 923.

Sugrue, M. F., Duff, N., and McIndewar, I. (1975). On the pharmacology of Org. 6368 (2β, 16β-dipiperidino-5α-androstan-3α-ol acetate dimethobromide), a new steroidal neuromuscular blocking agent. *J. Pharm. Pharmacol.*, **27**, 721.

INHIBITION DE LA CAPTATION NEURONALE DE NORADRENALINE DANS LE CŒUR PERFUSE ISOLE D'UN RAT AU MOYEN DE PANCURONIUM ET DE SES HOMOLOGUES, ORG. 6368, ORG. 7268 ET NC 45

RESUME

Les effets cardiovasculaires du pancuronium peuvent être le résultat partiel d'une interaction de cette substance sur le système nerveux sympathique. Nous avons examiné un mécanisme possible d'interaction, l'effet sur les processus de re-captation pour la noradrénaline. On a étudié une haute concentration (500 μmol litre^{-1}) de pancuronium et de ses homologues stéroïdiens très proches, Org. 6368, Org. 7268 et NC 45, du point de vue de l'inhibition de la captation de la noradrenaline tritiatée dans les sites neuronaux (Captation$_1$) et les sites extraneuronaux (Captation$_2$) d'un cœur perfusé isolé de rat. Toutes les substances testées provoquèrent une inhibition presque totale de la Captation$_1$. Les stéroides biquaternaires du pancuronium et l'Org. 6368 démontrèrent un caractère sélectif en ce qui concerne la Captation$_1$, les stéroides mono-quaternaires Org. 7268 et NC 45 provoquèrent également une inhibition significative de la Captation$_2$. On a fait une étude détaillée de l'inhibition de la Captation$_1$ en utilisant des concentrations moins fortes des composés. On a remarqué que les quatre stéroïdes provoquaient tous une inhibition de la Captation$_1$ qui dépendait de la concentration. Il est vraisemblable, par conséquent, que l'inhibition de la captation neuronal de la noradrénaline joue un rôle important dans l'étiologie des actions chronotropiques du pancuronium chez le rat.

INHIBIERUNG DER NEURONALEN AUFNAHME VON NORADRENALIN IM ISOLIERTEN, DURCHSCHWEMMTEN HERZ EINER RATTE DURCH PANCURONIUM UND DURCH ORG. 6368, ORG. 7268 UND NC 45

ZUSAMMENFASSUNG

Die Herzkreislaufwirkungen von Pancuronium können teilweise durch eine Wechselwirkung dieser Droge mit dem sympathischen Nervensystem bewirkt werden. Einen solchen moglichen Mechanismus der Wechselwirkung haben wir untersucht, und zwar die Wirkung des Wiederaufnahmeprozesses fur Noradrenalin. Pancuronium und seine eng verwandten steroiden Homologe, Org. 6368, Org. 7268 und NC 45 wurden in hohen Konzentrationen (500 μmol Liter^{-1}) studiert, was die Inhibierung der Aufnahme von tritiertem Noradrenalin in neuronalen Stellen (Aufnahme$_1$) und in extraneuronalen Stellen (Aufnahme$_2$) im isolierten, durchschwemmten Herz einer Ratte betrifft. Alle getesteten Drogen bewirkten eine fast totale Inhibierung der Aufnahme$_1$. Die doppelt quarternaren Steroide, Pancuronium und Org. 6368 waren selektiv für Inhibierung von Aufnahme$_1$, die mono-quarternaren Steroide, Org. 7268 und NC 45 bewirkten ebenfalls eine wesentliche Inhibierung von Aufnahme$_2$. Die Aufnahme$_1$-Inhibierung wurde detailliert mit Verwendung geringerer Konzentrationen der Droge untersucht. Alle vier Steroide bewirkten eine von der Konzentration abhängige Inhibierung von Aufnahme$_1$. Es ist daher wahrscheinlich, dass die Inhibierung der neuronalen Aufnahme von Noradrenalin eine wesentliche Rolle in der Ätiologie der chronotropischen Aktionen von Pancuronium in der Ratte spielt.

INHIBICION DE LA CAPTACION NEURONAL DE NORADRENALINA EN EL CORAZON PERFUSADO AISLADO DEL RATON MEDIANTE PANCURONIO Y SUS HOMOLOGOS, ORG. 6368, ORG. 7268 Y NC 45

SUMARIO

Los efectos cardiovasculares del pancuronio pueden ser parcialmente causados por una interacción de dicha substancia con el sistema nervioso simpático. Examinanos un posible mecanismo de interacción, el efecto sobre los procesos de re-captación de noradrenalina. Se procedió al estudio del pancuronio y de sus homólogos esteroides estrechamente relacionados, Org. 6368, Org. 7268 y NC 45 en una alta concentración (500 μm litro^{-1}) para inhibir la captación de noradrenalina tritiada dentro de los sitios neuronales (Captación$_1$) y de los sitios extraneuronales (Captación$_2$) en el corazón perfusado aislado del ratón. Todas las substancias bajo prueba ocasionaron una inhibición casi total de la Captación$_1$. Los esteroides bicuaternarios Pancuronio y Org. 6368 fueron selectivos para la inhibición de la Captación$_1$, los esteroides monocuaternarios Org. 7268 y NC 45 produjeron también una inhibición significativa de la Captación$_2$. Se realizó un estudio detallado de la inhibición de la Captación$_1$ mediante el uso de concentraciones menores de los compuestos. Se observó que los cuatro esteroides todos ocasionaban una inhibición de la Captación$_1$ que dependía de la concentración. Por lo tanto, es muy probable que la inhibición de la captación neuronal de noradrenalina juegue un papel importante en la etiología de las acciones cronotrópicas del pancuronio en los ratones.

Br. J. Anaesth. (1980), **52**, 319

EFFECTS OF TEMPERATURE, ADENOSINE TRIPHOSPHATE AND MAGNESIUM CONCENTRATIONS ON THE CONTRACTION OF ACTOMYOSIN ISOLATED FROM HALOTHANE-SENSITIVE AND -INSENSITIVE GERMAN LANDRACE PIGS

R. A. Green, G. Mitchell and J. J. A. Heffron

SUMMARY

The effects of temperature, adenosine triphosphate and magnesium on the calcium sensitivity of actomyosin were investigated on actomyosin obtained from six halothane-sensitive and five halothane-resistant German Landrace pigs. No difference in the contractile properties was found in actomyosin from the two types of pig. However, in both types calcium sensitivity of the actomyosin was lost at temperatures slightly greater than those occurring physiologically. Both ATP and Mg^{2+} protect against the loss of calcium sensitivity. These results suggest that the basic lesion in halothane-induced malignant hyperthermia does not lie in the contractile proteins. It is likely, however, that the decreases in intracellular ATP and Mg^{2+} concentrations which occur in pigs during malignant hyperthermia, contribute to the development of the syndrome.

Malignant hyperthermia (MH) is a rare syndrome occurring in humans exposed to certain anaesthetic agents, especially halothane. A similar or identical syndrome occurs in some breeds of pig (Britt and Kalow, 1970). MH is characterized by a rapid increase in body temperature ($>2\ ^\circ C\ h^{-1}$), lacticacidosis, muscle rigidity and death (Relton, Britt and Steward, 1973).

The site of the primary lesion is considered to be the skeletal muscle as this is the most likely source of heat, lactic acid and increased concentrations of serum creatine phosphokinase (c.p.k.) (de Villafranca and Waksmonski, 1970). A central cause has been eliminated on the basis of clinical findings (Britt and Kalow, 1970).

Until recently the emphasis of research has been on the sarcoplasmic reticulum (SR), which was thought to be especially sensitive to anaesthetic agents in susceptible individuals, the dominant theory being that the SR released calcium into the sarcoplasm in response to an effect of the triggering agent (Britt and Kalow, 1970; Hall, Lucke and Lister, 1975).

Increases in the calcium concentration (approximately 5×10^{-6} mol litre^{-1}) would account for the muscle rigidity, as a result of increased actomyosin interaction, activation of phosphorylase kinase, and an increase in the rate of glycolysis which could in turn account for the generation of heat and the production of lactate. However, the fact that membrane stabilizing agents, which affect calcium movements out of and into the SR cannot reverse the established syndrome, suggests that the SR is not the site of the primary lesion (Hall, Trim and Woolf, 1972; Mitchell and Heffron, 1975).

Recently, Fuchs (1975) suggested that there may be a loss of calcium sensitivity in the contractile proteins of sensitive muscle during MH rather than an increase in myoplasmic calcium concentrations. Fuchs (1975) and Fuchs, Hartshorne and Barns (1975) showed also that when the temperature was increased to slightly greater than that occurring physiologically, there was a loss of calcium dependence for the occurrence of superprecipitation in frog, rabbit and human muscle natural actomyosin (NAM). It has been shown also that increased concentrations of adenosine triphosphate (ATP) can "protect" against this loss of calcium sensitivity (Levy and Fleisher, 1965). Furthermore, it has been shown that halothane inhibits porcine mitochondrial respiration when NAD-linked substrates are used (Eikelenboom and van der Bergh, 1971). This could result in a reduction in ATP synthesis. Therefore, it seems possible that, if there is an underlying deficiency in the production of ATP, muscle contraction will occur independent of calcium concentrations, as the temperature increases.

R. A. Green, B.SC.; G. Mitchell, B.SC., B.V.SC., PH.D.; J. J. A. Heffron,* PH.D.; Departments of Physiology and Physiological Chemistry,* University of the Witwatersrand, Medical School, Hospital Street, Johannesburg.

Correspondence to G. Mitchell, Department of Physiology, School of Veterinary Science, Park Row, Bristol BS1 5LS (until December 31, 1980).

0007-0912/80/030319-05 $01.00

© Macmillan Journals Ltd 1980

In addition, Hall, Lucke and Lister (1975) have shown that infusions of Mg^{2+} can decrease the muscle rigidity characteristic of the syndrome. This suggests that Mg^{2+}, which leaks out of myoplasm during the syndrome (Berman et al., 1970), may play a regulatory role in excitation–contraction coupling, and its leakage could, therefore, precipitate contraction independent of the calcium concentration. This effect may also be temperature dependent.

Therefore, we have examined the effect of temperature on natural actomyosin (NAM) obtained from halothane-sensitive and -resistant pigs, and the effects of various concentrations of ATP and Mg^{2+} on the calcium sensitivity of excitation–contraction coupling.

MATERIALS AND METHODS

Natural actomyosin was prepared from 11 pigs (six halothane susceptible, five resistant), by extracting homogenized biopsied muscle with 4 volumes of a solution containing: potassium chloride 0.6 mol $litre^{-1}$, Tris–HCl 50 mmol $litre^{-1}$ (pH 7.5) and dithreital 1 mmol $litre^{-1}$ (DTT) for 24 h at 0–4 °C. This was followed by dilution with a further 4 volumes and centrifugation at 20 000 *g* for 30 min to remove non-solubilized material. The supernatant was diluted with 9 volumes of double-distilled water, and the actomyosin collected at 5000 *g* and resuspended in 3 volumes of a solution containing: Tris–HCl 25 mmol $litre^{-1}$ (pH 7.3), DTT 1 mmol $litre^{-1}$ and potassium chloride 0.6 mol $litre^{-1}$. The purification procedure was carried out twice. The protein concentration in the final suspension was measured by the biuret method with a bovine serum albumin standard and adjusted to 5 mg ml^{-1}. All preparations were glycerinated (50%) and stored at 0 °C until used.

Changes in turbidity associated with precipitation of actomyosin (Spicer and Gergely, 1951) were measured on a Beckman Acta C III spectrophotometer, at a wavelength of 660 nm and temperatures were monitored with a platinum resistance probe in one of the cuvettes. The incubation solution contained imidazole HCl 25 mmol $litre^{-1}$ (pH 7.1), potassium chloride 50 mmol $litre^{-1}$, DTT 1 mmol $litre^{-1}$, protein 0.2 mg ml^{-1}, 4% glycerol, ethylene glycol bis (β-aminoethyl ether) N,N,N',N'-tetra-acetic acid (EGTA) 0.8 mmol $litre^{-1}$, and calcium chloride 0.8 mmol $litre^{-1}$, magnesium sulphate and ATP as indicated.

Cuvette contents were continuously stirred magnetically to avoid settling of the precipitate. Percentage loss of calcium sensitivity was calculated using the response to ATP–Mg addition in the absence of calcium (EGTA added), and the maximum response when calcium was added.

Analytical grade reagents and double-distilled water were used throughout the experiment. ATP (disodium salt) was obtained from Boehringer.

RESULTS

Figure 1 shows a typical tracing of the superprecipitation phenomenon when full calcium sensitivity was retained. The response decreased after an initial rapid increase following the addition of calcium.

Figure 2 shows the percentage loss of calcium

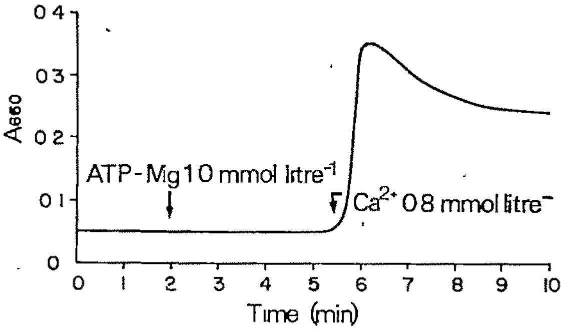


FIG. 1. A typical tracing of precipitation of actomyosin by calcium; temperature = 35 °C. The precipitation results in increased absorbance.

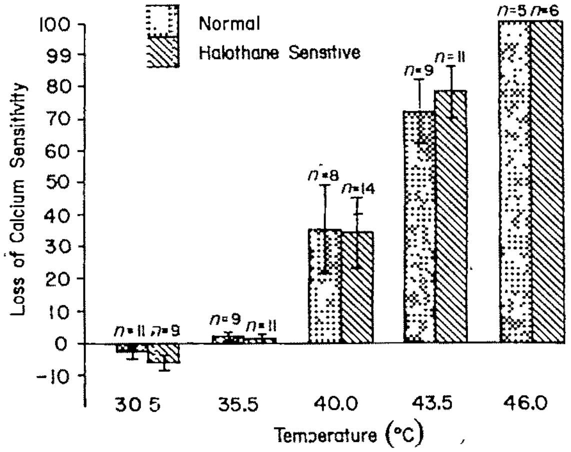


FIG. 2. The effect of temperature on calcium sensitivity. Each preparation of actomyosin contained ATP 1 mmol $litre^{-1}$ and Mg^{2+} 1 mmol $litre^{-1}$. The percentage loss of calcium sensitivity is shown as mean and standard error of the mean for all preparations at each temperature.

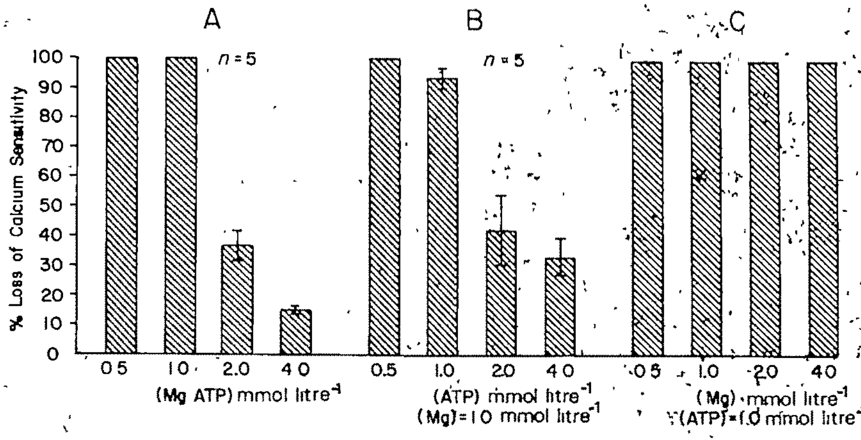


FIG. 3. The effects of varying concentrations of ATP + Mg on calcium sensitivity. Percentage loss of calcium was measured at a cuvette temperature of 43.5 °C.

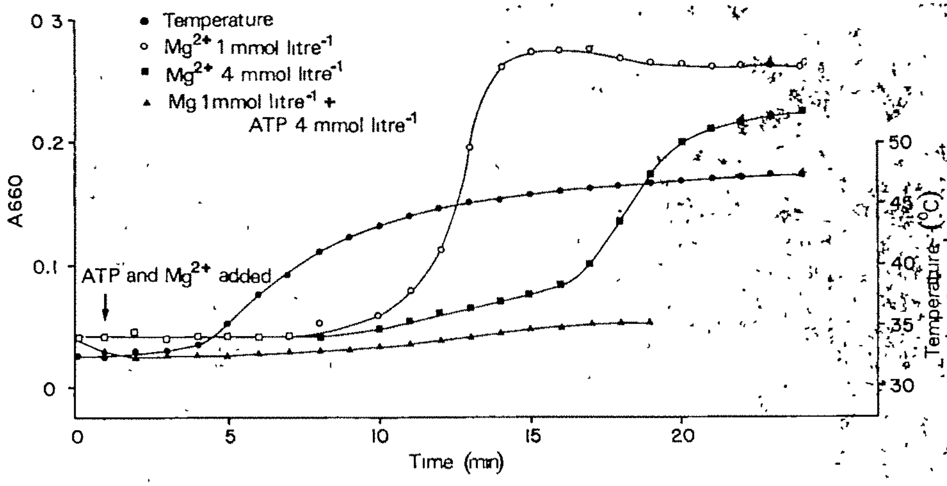


FIG. 4. The effect of Mg^{2+} on calcium sensitivity. The absorbance of the system was measured at 1-min intervals. Increased concentrations of magnesium delay the onset of precipitation.

sensitivity as temperature was increased from 30 to 46 °C in both halothane-sensitive and non-sensitive pigs. The large SEM at 40 °C is probably attributable to the proximity to the critical temperature at which a large change in calcium sensitivity occurs. Thus at this temperature, because of slight biological variation, a large range of responses resulted. There were no significant differences between the responses of sensitive and non-sensitive pigs at any temperature (*t* test).

Figure 3A shows the effect of different concentrations of magnesium–ATP on percentage loss of calcium sensitivity at a temperature of 43.5 °C. It is clear that increasing the concentration of Mg–ATP maintains calcium sensitivity.

Figure 3B shows the effects of different concentrations of ATP with a constant magnesium concentration (1 mmol litre^{-1}) at the same temperature. These results show that increasing ATP concentrations protected the actomyosin against temperature-induced calcium insensitivity.

Varying magnesium concentrations alone (fig. 3C) with a constant ATP concentration gave no protection against loss of calcium sensitivity. Thus at 43.5 °C ATP conferred protection against loss of calcium sensitivity, whereas magnesium did not.

However, figure 4 shows a typical result found when the temperature of the cuvettes was allowed to increase from approximately 30 °C to approximately 50 °C in the absence of calcium but with ATP 1 mmol litre^{-1} added. Suspensions containing magnesium 4 mmol litre^{-1} underwent superprecipitation at greater temperatures than those with magnesium 1 mmol litre^{-1}. These critical temperatures (estimated as the temperature at which 50% superprecipitation occurs) for the five pigs tested are shown in table I.

TABLE I. *Critical temperatures for solutions containing magnesium* 1.0 *mmol litre*$^{-1}$ *and* 4.0 *mmol litre*$^{-1}$. **Preparation obtained from halothane-sensitive pigs*

Preparation	Temperatures (°C) Mg^{2+} 1 mmol litre^{-1}	 Mg^{2+} 4 mmol litre^{-1}
1*	43.5	45.0
2	44.8	46.3
3	45.0	46.3
4	45.0	46.3
5*	42.5	44.0

The differences in temperatures were significant at the 5% level (Wilcoxon test) for all pigs tested, but there were no significant differences between halothane-susceptible and -resistant pigs, although critical temperatures for sensitive pigs were clearly less than those for insensitive pigs. Figure 4 shows also that, in the presence of adequate ATP (4 mmol litre^{-1}), superprecipitation did not occur as the temperature increased, even if Mg^{2+} concentrations were small (1 mmol litre^{-1}).

DISCUSSION

These results show that NAM isolated from pig muscle behaved in the same way as that of frog, rabbit and human muscle (Fuchs, Hartshorne and Barns, 1975) in that it lost its sensitivity to calcium at temperatures greater than those occurring physiologically.

In addition, the data indicate that the basic lesion in this syndrome does not lie in the contractile proteins as there are no significant differences between halothane-susceptible and -resistant pigs (fig. 2). However, the results suggest that, although the contraction mechanism is similar in all pigs and is dependent on adequate ATP and Mg^{2+} concentrations for proper functioning, disturbances in the concentrations of ATP and Mg^{2+} will lead to malfunctioning. Further, the results show that the effects of aberrant ATP and Mg^{2+} concentrations are potentiated as the temperature increases. It is clear that at greater temperatures adequate ATP (4 mmol litre^{-1} fig. 4) prevents superprecipitation. However, if ATP concentrations are inadequate, then loss of Mg^{2+} will cause superprecipitation at lower temperatures.

It has been shown that during the syndrome muscle ATP concentrations are small (Isaacs and Heffron, 1975) or decline and that Mg^{2+} leaks out of the myoplasm into the plasma (Berman et al., 1970). Hyperthermia is a characteristic of the syndrome. Therefore, it is conceivable that the rigor in MH is initiated or potentiated by a loss in calcium sensitivity as a result of reduced muscle ATP and Mg^{2+} and hyperthermia which occurs during the syndrome.

In these circumstances attempts to reverse the established syndrome by decreasing myoplasmic calcium concentrations must be futile. On the other hand, as reported by Hall, Lucke and Lister (1975), infusions of Mg^{2+} will tend to reverse rigidity. Apart from the apparent protecting effect of Mg^{2+} alone on loss of calcium sensitivity (table I), Mg^{2+} infusions will also depress glycolysis, stimulate oxidative phosphorylation and increase uptake by SR (Relton, Britt and Steward, 1973).

All these observations suggest that, although the contractile proteins are not the site of the basic lesion in MH, they become involved secondarily, lose their calcium sensitivity and potentiate an already uncontrollable reaction.

REFERENCES

Berman, M. C., Harrison, G. G., Bull, A. B., and Kench, J. E. (1970). Changes underlying halothane-induced malignant hyperpyrexia in Landrace pigs. *Nature (Lond.)*, **225**, 653.

Britt, B. A., and Kalow, W. (1970). Malignant hyperthermia aetiology unknown. *Can. Anaesth. Soc. J.*, **17**, 316.

Eikelenboom, G., and van der Berg, S. G. (1971). Aberrant mitochondrial energy metabolism in stress-susceptible pigs, in *Second International Symposium on Condition and Meat Quality in Pigs* (eds J. C. M. Hassel-de-Heer, G. R. Schmidt, W. Sybesma and others), p. 66. Wageningen, Holland: Pudock Press.

Fuchs, F. (1975). Thermal inactivation of the calcium regulatory mechanism of human skeletal muscle actomyosin: a possible contributing factor in the rigidity of malignant hyperthermia. *Anesthesiology*, **42**, 584.

—— Hartshorne, D. J., and Barnes, E. M. (1975). ATPase activity and superprecipitation of skeletal muscle actomyosin of frog and rabbit: effect of temperature on calcium sensitivity. *Comp. Biochem. Physiol.*, **51B**, 165.

Hall, G. M., Lucke, J. M., and Lister, D. (1975). Treatment of malignant hyperthermia. *Anaesthesia*, **30**, 308.

Hall, L. W., Trim, C. M., and Woolf, N. (1972). Further studies of porcine malignant hyperthermia. *Br. Med. J.*, **2,** 145.

Isaacs, H., and Heffron, J. J. A. (1975). Morphological and biochemical defects in muscle of human carriers of the MH syndrome. *Br. J. Anaesth.*, **47,** 475.

Levy, H. M., and Fleisher, M. (1965). Studies of the superprecipitation of actomyosin suspension as measured by change in turbidity. I: Effects of adenosine triphosphate concentration and temperature. *Biochim. Biophys. Acta*, **100,** 479.

Mitchell, G., and Heffron, J. J. A. (1975). Procaine in porcine malignant hyperthermia. *Br. J. Anaesth.*, **47,** 667.

Relton, J. E. S., Britt, B. A., and Steward, D. J. (1973). Malignant hyperpyrexia. *Br. J. Anaesth.*, **45,** 269.

Spicer, S. S., and Gergely, J. (1951). Studies on the combination of myosin and actin. *J. Biol. Chem.*, **188,** 179.

de Villafranca, G. W., and Waksmonski, C. A. (1970). Superprecipitation of horseshoe crab and rabbit myosin B. *Int. J. Biochem.*, **1,** 29.

EFFETS DE LA TEMPERATURE ET DES CONCENTRATIONS DU TRIPHOSPATE D'ADENOSINE ET DE MAGNESIUM SUR LA CONTRACTION DE L'ACTOMYOSINE PRELEVEE SUR DES COCHONS SENSIBLES A L'HALOTHANE ET SUR DES COCHONS LANDRACE ALLEMANDS QUI Y SONT INSENSIBLES

RESUME

On a fait des recherches sur l'actomyosine obtenue de six cochons sensibles à l'halothane et de cinq cochons Landrace allemands résistants à l'halothane, pour étudier les effets de la température, du triphosphate d'adénosine et du magnésium sur la sensibilité au calcium de l'actomyosine. On n'a trouvé dans l'actomyosine émanant des deux types de cochons aucune différence dans les propriétés contractiles. Quoi qu'il en soit, la sensibilité au calcium de l'actomyosine a été, dans les deux types, perdue à des températures légèrement supérieures à celles qui se produisent physiologiquement. L'ATP tout comme le Mg^{2+} protègent contre la perte de sensibilité au calcium. Les résultats obtenus laissent penser que la lésion de base qui se produit dans l'hyperthermie maligne provoquée par l'halothane ne se trouve pas dans les protéines contractiles. Il est toutefois probable que les diminutions dans les concentrations intracellulaires d'ATP et de Mg^{2+} qui se produisent chez les cochons pendant l'hyperthermie maligne contribuent au développement du syndrome.

WIRKUNGEN VON TEMPERATUR, ADENOSINTRIPHOPHAT UND MAGNESIUM AUF DIE KONTRAKTION VON ACTOMYOSIN AUS HALOTHANEMPFINDLICHEN UND HALOTHANUNEMPFINDLICHEN DEUTSCHEN LANDRACE-SCHWEINEN

ZUSAMMENFASSUNG

Die Wirkungen von Temperatur, Adenosintriphophat und Magnesium auf die Kalziumempfindlichkeit von Actomyosin wurden bei Actomyosin untersucht, das aus sechs halothanempfindlichen und fünf halothanunempfindlichen deutschen Landrace-Schweinen entnommen wurde. Im Actomyosin aus beiden Gruppen von Schweinen fand man keine Unterschiede der Kontraktionseigenschaften. Bei beiden Gruppen aber ging die Kalziumempfindlichkeit bei Temperaturen verloren, die leicht uber den physiologisch gegeben lagen. Sowohl ATP und Mg^{2+} schützen vor dem Verlust von Kalziumempfindlichkeit. Diese Resultate zeigen, dass die grundlegende Läsion bei durch Halothan bewirkter, maligner Hyerthermie nicht in den kontraktilen Proteinen liegt. Es ist aber warhscheinlich, dass das Absinken intrazellulärer ATP-und Mg^{2+}-Konzentrationen, zu dem es bei Schweinen während maligner Hyperthermie kommt, zur Entwicklung des Syndroms beitragt.

EFECTOS DE LA TEMPERATURA, CONCENTRACIONES DEL TRIFOSFATO DE ADENOSINA Y DE MAGNESIO SOBRE CONTRACCION DE ACTOMIOSINA AISLADA A PARTIR DE PUERCOS ALEMANES LANDRACE SENSIBLES E INSENSIBLES AL HALOTANO

SUMARIO

Se averiguó los efectos de la temperatura, del trifosfato de adenosina y del magnesio sobre la sensibilidad al calcio de la actomiosina mediante actomiosina obtenida a partir de seis puercos alemanes Landrace sensibles al halotano y cinco resistantes al mismo. No se observaron diferencias algunas en las propiedades contractiles de la actomiosina de los dos tipos de puercos. Sin embargo, en ambos tipos, se perdió la sensibilidad al calcio de la actomiosina a temperaturas ligeramente más altas que las que ocurren fisiológicamente. Ambos el ATP y el Mg^{2+} protegen contra la pérdida de sensibilidad al calcio. Estos resultados hacen pensar que la lesión básica de la hipertermia maligna inducida por halotano no se debe a las proteinas contractiles. Sin embargo es probable que las reducciones de las concentraciones intracelulares en ATP y Mg^{2+} que ocurren en los puercos en el curso de la hipertermina maligna contribuyan al desarrollo del síndrome.

Br. J. Anaesth. (1980), **52**, 325

THE NATURE OF GENTAMICIN-INDUCED NEUROMUSCULAR BLOCK

T. TORDA

SUMMARY

Gentamicin in concentrations of 0.05–0.2 mmol litre^{-1} blocked neuromuscular transmission in the toad sartorius nerve–muscle preparation by decreasing the release of transmitter. In concentrations of 0.5–1 mmol litre^{-1} it decreased the amplitude of the miniature end-plate current by a curare-like action, without affecting the mean open channel lifetime

Antibiotic-induced neuromuscular blockade has been reported in patients following the use of aminoglycosides, tetracyclines, polymixins and colistin, and lincomycin (Pittinger and Adamson, 1972). In clinical practice, the aminoglycosides are the most frequent cause of such problems (Pittinger, Eryason and Adamson, 1970). Previous studies with neomycin have demonstrated a decrease in the postjunctional acetylcholine sensitivity and a magnesium-like action on the nerve terminal (Elmquist and Josefsson, 1962). Tissue-bath experiments using the phrenic nerve–diaphragm preparation, followed by bioassay of the acetylcholine in the bath fluid, have also shown a decrease in the release of acetylcholine in the presence of neomycin or gentamicin (Vital Brazil and Prado-Franceschi, 1969). However, experiments of this type are difficult to interpret as much of the acetylcholine release is consequent on the presence of added anticholinesterases, which are necessary to prevent the hydrolysis of acetylcholine during the experiments (Torda, 1978). Therefore, a series of experiments was undertaken to define the action of an aminoglycoside antibiotic at the neuromuscular junction. As gentamicin is at present the most commonly used member of this group in our hospitals, it was chosen for these experiments.

To define the prejunctional effects, the quantal content of the end-plate potential (e.p.p.) was measured. For the postjunctional effects the membrane potential was measured, miniature end-plate potentials (m.e.p.p.) and miniature end-plate currents (m.e.p.c.) were recorded, and their time course examined.

METHODS

The experiments were performed on the excised sartorius nerve–muscle preparation of the toad, *Bufo marinus*, at 21 ± 1 °C. A hypertonic Ringer's solution was used throughout, to increase the frequency of the m.e.p.p. It contained sodium chloride 140 mmol litre^{-1}, potassium chloride 2.5 mmol litre^{-1}; calcium chloride 1.8 mmol litre^{-1} and sodium phosphate buffer (pH 7.2) 3 mmol litre^{-1}.

Membrane potential, m.e.p.p. and e.p.p. were recorded through glass microelectrodes of 10–20 MΩ impedance filled with potassium chloride 2.5 mol litre^{-1}. The signals were amplified, passed through an analog delay unit and averaged on a "Neurolog" averager. The average of 64–256 potentials was then printed out on a chart recorder. When e.p.p. were recorded a calibration signal of 1 mV and 10 ms duration was also injected into the system, about 50–70 ms after the nerve stimulus. In the latter experiments the nerve was stimulated through a suction electrode at 1 Hz with supramaximal square wave pulses of 100 μs duration. To eliminate the stimulus artefact the polarity of the stimulator pulse was reversed half way through the averaging process. Figure 1 shows schematically the experimental set-up. The quantal content was calculated from the ratio of e.p.p. to m.e.p.p. and as the e.p.p. were of low amplitude, no correction for non-linear summation was made.

M.e.p.c. were recorded extracellularly through electrodes filled with sodium chloride 3 mol litre^{-1} in agar. Details of the technique have been described elsewhere (Gage and McBurney, 1975; Torda and Gage, 1977). M.e.p.c. were recorded on FM tape and

---

T. A. TORDA, M.D., F.F.A.R.A.C.S., Schools of Surgery, and Physiology and Pharmacology of the University of New South Wales. Present address: Division of Anaesthesia and Intensive Care, Prince Henry Hospital, Little Bay, N.S.W. 2036, Australia.

0007–0912/80/030325–05 $01.00

© Macmillan Journals Ltd 1980

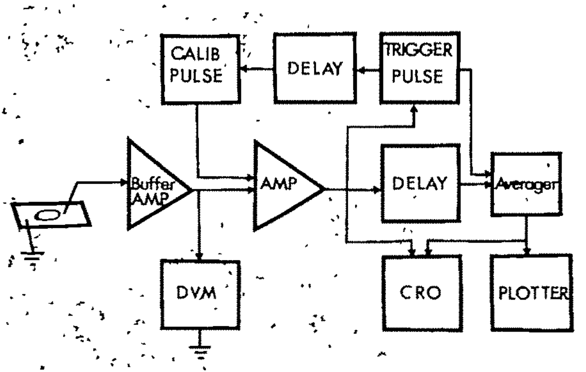


FIG. 1. Block diagram of the apparatus used to determine the quantal content of the end-plate potential.

processed later through a computer which measured the growth time (20–80%), amplitude and time constant of decay. In the experiments, observations were made at the same end-plate in control and drug solutions, and again after return to the control solution.

RESULTS

Miniature end-plate potentials

M.e.p.p. alone were recorded in five experiments: two in gentamicin 1.0 mmol litre^{-1}, two in gentamicin 0.5 mmol litre^{-1} and one in gentamicin 0.3 mmol litre^{-1}. In these experiments e.p.p. recording was attempted, but there was total block of acetylcholine release except in the 0.3-mmol litre^{-1} solution where an occasional e.p.p. was seen. The m.e.p.p. amplitude was reduced at all concentrations (table I). The large decrease caused by the 0.5-mmol litre^{-1} solution probably reflected an unusually sensitive preparation, as both experiments were performed on different end-plates of the same muscle. The time course of the m.e.p.p. was not changed by the gentamicin and there was no effect on the resting membrane potential.

TABLE I. *The effect of gentamicin 0.3, 0.5 and 1.0 mmol litre^{-1} on the amplitude of miniature end-plate potentials*

	No. of cells	No. of m.e.p.p.	Amplitude mV	Amplitude %
Control	2	64	1.33	
Gentamicin 0.3		64	0.76	57
Control	2	64	1.25	
Gentamicin 0.5		96	0.44	35
Control	1	64	1.60	
Gentamicin 1.0		64	0.72	45

Quantal content

The quantal content of the e.p.p. was measured at four end-plates in each of three solutions containing gentamicin 0.05, 0.1 and 0.2 mmol litre^{-1}. It was found to be decreased in a concentration-dependent manner (table II). As stated above, gentamicin 0.3 mmol litre^{-1} caused near complete block of evoked transmitter release. Greater concentrations blocked release completely. The resting membrane potential was unchanged.

Miniature end-plate currents

M.e.p.c. were recorded from 11 end-plates in control solution and solutions containing gentamicin

TABLE II. *The effect of gentamicin on the quantal content of the end-plate potential*

Concentration (mmol litre^{-1})	No. of cells	Quantal content (mean ± SEM)
0.05	4	2.91 ± 0.36
0.1	4	2.34 ± 0.41
0.2	4	1.02 ± 0.13

TABLE III. *Summary of the effects of gentamicin 0.1, 0.5 and 1.0 mmol litre^{-1} on miniature end-plate currents; on the growth time 20–80%, amplitude and time constant of decay. Gentamicin concentration is in mmol litre^{-1}. Results are given as mean ± SEM. Amplitude is in arbitrary units. Statistical significance of the differences: *$P < 0.001$; **$P < 0.05$*

	No of cells	No. of m.e.p.c.	Growth time µs	Growth time %	Amplitude units	Amplitude %	Time constant of decay ms	Time constant of decay %
Control	2	74	507 ± 61		167 ± 3		3.14 ± 12	
Gentamicin 0.1		45	617 ± 74	122	154 ± 5**	93	3.05 ± 16	97
Control	4	139	342 ± 16		197 ± 3		2.47 ± 3	
Gentamicin 0.5		110	503 ± 44*	147	165 ± 3*	84	2.67 ± 5	106
Control	5	196	325 ± 14		323 ± 3		2.70 ± 6	
Gentamicin 1.0		149	670 ± 30*	206	178 ± 4*	55	2.78 ± 6	103

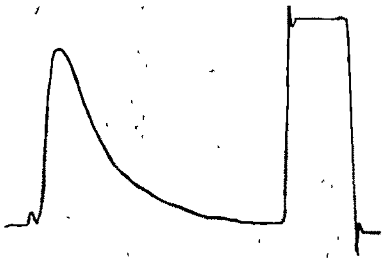


FIG. 2. The average of 128 end-plate potentials. The square wave near the tail of the e.p.p. is a 1-mV, 10-ms calibration signal.

0.1, 0.5 and 1.0 mmol litre^{-1} (table III). Gentamicin prolonged the growth time of the m.e.p.c. and reduced their amplitude without detectable effect on the time-course of the decay phase. Rounding of the current peaks as seen with anticholinesterases was not observed.

DISCUSSION

Before discussing these results it may be appropriate to write a few words about the methods used, which may not be familiar to some anaesthetists. Failure of neuromuscular transmission can occur from interruption of any link in the normal chain of events. This can be interruption of the spread of the nerve action potential on to the terminal filaments, failure of transmitter release, failure of transmitter receptor combination (e.g. tubocurarine block), or failure of normal ionic channel function as is the case with general anaesthetics, which cause premature closure or block of the channels (Adams, 1976). Increase of the threshold of depolarization at which a self-propagating action potential is generated is also possible, but does not seem to be the mode of action of any clinically significant neuromuscular blocking agent. The final possible cause of neuromuscular failure is excitation–contraction uncoupling as by dantrolene (Franz, 1975).

In determining the mode of action of a neuromuscular blocking drug two key processes can be studied. The first is the quantal content of the e.p.p., that is the number of quanta of transmitter released by the nerve action potential. The e.p.p. is recorded through an intracellular electrode, but in order to do this contraction of the cell must be prevented. Increasing the magnesium in the perfusing fluid does this by decreasing the quantal content to a subthreshold value (del Castillo and Katz, 1954), after which any further decrease would be caused by the test drug. Cutting the cell near the neuromuscular junction causes the membrane potential to decrease and stops contraction (Hubbard and Wilson, 1973). Unfortunately the decrease tends to be progressive and a stable situation is hard to maintain during experiments. Tubocurarine blocks acetylcholine receptors and stops a preparation contracting. However, it has an effect also on transmitter release, which is still the subject of debate (Auerbach and Betz, 1971; Galindo, 1971). Finally, one can apply the test drug in sufficient concentration to stop contraction and look for decreases in quantal content. To be significant in causing neuromuscular blockade, this decrease must be quite marked as the normal nerve terminal releases three to four times more transmitter than is necessary for transmission (Chang, 1978).

The quantal content can be calculated from the e.p.p. in one of three ways (del Castillo and Katz, 1954), from the ratio of the square of the mean e.p.p. amplitude to its variance, from the natural logarithm of the number of trials to the number of "failures", that is zero quantum e.p.p., or directly from the ratio of the mean e.p.p. to the mean m.e.p.p. (which is the potential in response to a single quantum). The first two methods assume that the probability of release of a transmitter quantum is a Poisson function, which may not be true (Wernig, 1975). The last method makes no such assumption but may need correction for non-linear summation of the quantal responses (Martin, 1955). Where the e.p.p. is small in comparison with the membrane potential, this error is negligible.

During intracellular recording of e.p.p. or m.e.p.p. the membrane potential is usually observed continuously as the amplitude of both is affected by it.

The m.e.p.c. is the current evoked by a single quantum of transmitter. It gives a measure of the responsiveness of the postjunctional portion of the transmission mechanism. Its amplitude reflects the number of open ionic channels and their individual conductance. It normally decays in an exponential manner and the time constant of decay (the time taken to fall to 1/e or by 63%) is equal to the average life-time of the open channel (Anderson and Stevens, 1973). The time constant is affected by temperature, membrane potential and possibly by the fluidity of the surrounding lipid (Gage and Hamill, 1976). Certain substances, such as general or local anaesthetics, can block open channels and decrease the charge transfer across the postjunctional membrane in response to the quanta of transmitter. The rate constants of the blocking and unblocking reactions and that governing the closure of the unblocked channel determine whether the decay phase remains a single exponential or becomes biphasic (Adams, 1976). Two techniques are available for recording the m.e.p.c. In "voltage clamping" (Takeuchi and Takeuchi, 1959) a second, current electrode is inserted into the same cell in which the recording electrode is lodged. Current is then injected into the cell to maintain a constant potential, and this current is equal to the physiological currents generated. As the potential across the junctional membrane can be altered during such experiments, the technique is capable not only of recording physiological currents, but also of exploring their variation with changes in membrane potential. The disadvantage of this technique lies in the necessity of placing the two electrodes in very close proximity, otherwise, because of spatial decay of the currents, the injected current will not reflect accurately the physiological events. The alternative technique is that of extracellular recording. The technique is simple and the record of the time-course of m.e.p.c. is accurate. However, the potential generated by the current is a function of the impedance between cell and electrode and therefore any change in electrode pressure during an experiment will alter the recorded amplitude of the currents (Gage, 1976). A second source of inaccuracy in amplitude measurement can arise when the currents are "captured" by a recording device which is triggered by a potential of pre-set amplitude. If the amplitude of the potentials generated by the m.e.p.c. decreases, the proportions which fail to trigger the device will increase and there will be a selection of the larger peaks. This gives the technique a tendency to underestimate decreases in amplitude. During extracellular recording the membrane potential is not monitored. As decrease in membrane potential, which may occur during an experiment, will shorten the time constant of decay, it is a good technique to record some control currents after as well as before drug treatment.

Therefore, from the results in the previous section the following conclusions can be drawn. In the toad, gentamicin is a more potent blocker of neuromuscular transmission than in the mouse, by a factor of 20 or more (Singh, Harvey and Marshall, 1978). At the toad sartorius neuromuscular junction a concentration of 0.05 mmol litre^{-1} was sufficient to prevent contraction in response to supramaximal nerve stimuli. Concentrations in the range 0.05–0.2 mmol litre^{-1} caused severe reduction in the quantal content of the e.p.p. Concentrations of 0.3 mmol litre^{-1} or more prevented the e.p.p. Thus, gentamicin blocks neuromuscular transmission by a prejunctional action, preventing transmitter release. As calcium increases transmitter release at the neuromuscular junction (Dodge and Rahaminoff, 1967) it can be expected to antagonize gentamicin-induced blockade, as has been demonstrated by Singh, Harvey and Marshall (1978).

The m.e.p.c. showed slowing of the growth time and decreases in amplitude under the influence of gentamicin. These effects occurred only at concentrations an order of magnitude greater than that necessary for neuromuscular block. The time constant of decay of the m.e.p.c. (the mean open channel lifetime) was not altered. This postjunctional effect therefore resembles tubocurarine, which blocks acetylcholine receptors, rather than that of anaesthetics, which reduce channel lifetime (Gage and Hamill, 1976; Torda and Gage, 1977). No explanation for the slowing of the m.e.p.c. growth phase can be offered. It could be a result of reduction of the rate of the transmitter–receptor combination or that of the activated receptor-channel opening reaction. The finding is unusual, but these experiments do not enable one to distinguish between the two possibilities. Unlike the prejunctional action, the postjunctional effect of gentamicin does not appear to be of practical significance.

ACKNOWLEDGEMENTS

I am indebted to Professor P. W. Gage for continued help and support. Miss M. Lonregan assisted with some of the experiments.

REFERENCES

Adams, P. R. (1976). Drug blockage of open end-plate channels. *J. Physiol.* (*Lond.*), **260**, 531.

Anderson, C. R., and Stevens, C. F. (1973). Voltage clamp analysis of acetylcholine produced end-plate current fluctuations at frog neuromuscular junctions. *J. Physiol.* (*Lond.*), **235**, 655.

Auerbach, A., and Betz, J. (1971). Does curare affect transmitter release? *J. Physiol.* (*Lond.*), **213**, 691.

del Castillo, J., and Katz, B. (1954). Quantal components of the end-plate potential. *J. Physiol.* (*Lond.*), **124**, 560.

Change, C. C. (1978). Use of alpha- and beta-bungarotoxins for the study of neuromuscular transmission. *Anesthesiology*, **48**, 309.

Dodge, F. A., and Rahaminoff, R. (1967). Co-operative action of calcium ions in transmitter release at the neuromuscular junction. *J. Physiol.* (*Lond.*), **193**, 419.

Elmquist, D., and Josefsson, J. O. (1962). The nature of neuromuscular block produced by neomycine. *Acta Physiol. Scand.*, **54**, 105.

Franz, D. N. (1975). *The Pharmacological Basis of Therapeutics*, 5th edn (eds L. S. Goodman and A. Gilman), p. 241. New York: Macmillan.

Gage, P. W. (1976). Generation of end-plate potentials. *Physiol. Rev.*, **56**, 177.

—— Hamill, O. (1976). Effects of several inhalation anaesthetics on the kinetics of postsynaptic conductance changes in mouse diaphragm. *Br. J. Pharmacol.*, **57**, 263.

—— McBurney, R. N. (1975). Effects of membrane potential, temperature and neostigmine on the conductance change caused by a quantum of acetylcholine at the toad neuromuscular junction. *J. Physiol. (Lond.)*, **244**, 385.

Galindo, A. (1971). Prejunctional effect of curare: its relative importance. *J. Neurophysiol.*, **34**, 289.

Hubbard, J. I., and Wilson, D. F. (1973). Neuromuscular transmission in a mammalian preparation in the absence of blocking drugs and the effect of d-tubocurarine. *J. Physiol. (Lond.)*, **228**, 307.

Martin, A. R. (1955). A further study of the statistical composition of the end-plate potential. *J. Physiol. (Lond.)*, **130**, 114.

Pittinger, C., and Adamson, R. (1972). Antibiotic blockade of neuromuscular function. *Ann. Rev. Pharmacol.*, **12**, 169.

—— Eryason, Y., and Adamson, R. (1970). Antibiotic-induced paralysis. *Anesth. Analg. (Cleve.)*, **49**, 487.

Singh, Y. N., Harvey, A. L., and Marshall, I. G. (1978). Antibiotic-induced paralysis of the mouse phrenic nerve–hemidiaphragm preparation, and reversibility by calcium and neostigmine. *Anesthesiology*, **48**, 418.

Takeuchi, A., and Takeuchi, N. (1959). Active phase of frog's end-plate potential. *J. Neurophysiol.*, **22**, 395.

Torda, T. A. (1978). The effects of some drugs at the mammalian neuromuscular junction. M.D. Thesis, University of N.S.W., p. 117.

—— Gage, P. W. (1977). Postsynaptic effect of i.v. anaesthetic agents at the neuromuscular junction. *Br. J. Anaesth.*, **49**, 771.

Vital Brazil, O., and Prado-Franceschi, J. (1969). The nature of neuromuscular block produced by neomycin and gentamycin. *Arch. Int. Pharmacodyn. Ther.*, **179**, 78.

Wernig, A. (1975). Estimates of statistical release parameters from crayfish and frog neuromuscular junctions. *J. Physiol. (Lond.)*, **244**, 207.

NATURE DU BLOCAGE NEUROMUSCULAIRE PROVOQUE PAR LA GENTAMICINE

RESUME

La gentamicine en concentration de 0,05–0,2 mmol litre^{-1} a bloqué la transmission neuromusculaire dans une préparation de muscle–nerf couturier de crapaud, en diminuant la libération du transmetteur. En concentrations de 0,5–1 mmol litre^{-1}, elle a diminué l'amplitude du courant de la plaque d'extrémité miniature par une action semblable à celle du curare, sans affecter la durée de vie moyenne du canal ouvert.

DAS WESEN DER VON GENTAMICIN BEWIRKTEN NEUROMUSKULÄREN BLOCKIERUNG

ZUSAMMENFASSUNG

Gentamicin in Konzentrationen von 0,05–0,2 mmol Liter^{-1} blockierte die neuromuskuläre Übertragung in einem Sartorius–Nerven/Muskelpraparat einer Krote, indem die Freigabe von Mittlersubstanz verringert wurde. In Konzentrationen von 0,5–1 mmol Liter^{-1} Gentamicin wurde die Amplitude des Miniatur-Endplattenstromes durch eine Curareahnliche Aktion gesenkt, ohne dabei die mittlere Kanalöffnungszeit zu beeinträchtigen.

NATURALEZA DEL BLOQUEO NEUROMUSCULAR INDUCIDO POR GENTAMICINA

SUMARIO

La gentamicina en concentraciones de 0,05–0,2 mmol litro^{-1} bloqueó la transmisión neuromuscular en la preparación nervio–músculo sartorio del zapo al disminuir la liberación del transmisor. En concentraciones de 0,5–1 mmol litro^{-1}, tuvo por efecto de disminuir la amplitud de la corriente de placa terminal miniature por una acción similar al del curare, sin afectar el tiempo de vida medio del canal abierto.

Br. J. Anaesth. (1980), 52, 331

TIME-COURSE OF FORMATION OF VOLATILE REDUCTIVE METABOLITES OF HALOTHANE IN HUMANS AND AN ANIMAL MODEL

G. K. GOURLAY, J. F. ADAMS, M. J. COUSINS AND J. H. SHARP

SUMMARY

The time-course of the formation of 2-chloro-1,1,1-trifluoroethane (CTF) and 2-chloro-1-1-difluoroethylene (CDF), two recently identified volatile reductive metabolites of halothane, has been studied in four patients receiving 1% halothane with 99% oxygen. The concentrations of CTF and CDF in end-expired breath increased with time and reached a plateau after approximately 60 min from commencing administration. A similar time-course and plateau was seen when Fischer 344 rats were anaesthetized with halothane 1% in oxygen. However, there was an eight-fold and 12-fold increase in CTF and CDF concentrations respectively when halothane 1% was administered under conditions of mild hypoxia (oxygen 14% inspired) to rats pretreated with phenobarbitone (this results in a marked increase in serum alanine aminotransferase (ALT) and necrotic damage in the vicinity of the central veins of the liver). It is suggested that breath concentrations of CDF and CTF provide a sensitive method of monitoring the reductive metabolism of halothane.

It has been shown previously (Cohen et al., 1975) that the metabolism of halothane in man results in the formation of trifluoroacetic acid (TFA), a TFA–ethanolamide conjugate and a 2-bromo-2-chloro-1,1-difluoro-ethylene–glutathione conjugate. It was thought likely that this last metabolite was formed by a *reductive* pathway whereas the other two were formed by an oxidative pathway. It is well known that the other oxidative metabolite is inorganic bromide.

More recently, however, Mukai and colleagues (1977) have shown in rabbits that halothane is metabolized to produce 2-chloro-1,1-difluoroethylene (CDF) and 2-chloro-1,1,1-trifluoroethane (CTF). These studies were extended to man by Sharp, Trudell and Cohen (1979) and small concentrations of these two new metabolites were detected in breath samples collected after the termination of halothane anaesthesia. Further, these authors proposed that the two new metabolities (CDF and CTF) were formed by an alternative *reductive* pathway.

Cousins and co-workers (1979) have described an animal model (Fischer 344 rat) in which both the oxidative and reductive metabolism of halothane were similar to that in man. In the presence of oxygen 100%, CDF and CTF were detected in similar amounts in both man and the model. Pretreatment in the model with phenobarbitone and the administration of halothane under conditions of mild hypoxia (oxygen 14%) resulted in at least a four-fold increase in reductive metabolism which was associated with a 10-fold increase in serum alanine aminotransferase (ALT) and centrilobular hepatic necrosis which was similar to the lesion described in patients diagnosed as having "halothane hepatitis".

The present communication reports the time-course of the formation of both CDF and CTF in man and an animal model of "halothane hepatitis". These metabolites may provide a sensitive means of monitoring the reductive metabolism of halothane which is assuming increasing importance in the aetiology of halothane-associated liver damage.

METHODS

Human studies

Four female patients, ASA status 1–2, with an age range of 26–47 yr were admitted to the study after informed consent had been obtained. The procedures included two elective operations (hysterectomy) (weight of patients, 56 and 73 kg) and two gastric bypass operations for obesity (weight of patients 123 and 130 kg).

Anaesthetic management. Anaesthesia was induced with sufficient thiopentone to obtund the eyelash reflex and the trachea was intubated following the administration of suxamethonium 1 mg kg^{-1}. Anaesthesia was maintained with 1% halothane in oxygen

---

GEOFFREY K. GOURLAY, B.PHARM., PH.D.; JOHN F. ADAMS, B.SC.(HONS); MICHAEL J. COUSINS, M.D., F.F.A.R.A.C.S., F.F.A.R.C.S.; J. HOWARD SHARP, B.SC., PH.D.; Department of Anaesthesia and Intensive Care, Flinders Medical Centre, Adelaide, South Australia 5042, Australia.
Correspondence to G. K. G.

0007–0912/80/030331–06 $01.00

© Macmillan Journals Ltd 1980

for the times specified in the Results section and neuromuscular blockade was produced with pancuronium 10 mg/70 kg. Ventilation was adjusted to maintain Pa_{CO_2} in the normal range. The dose of halothane was determined by multiplying the alveolar concentration (1 MAC) by time of administration (Cousins and Mazze, 1973); dosage ranged from 1½ to 2 MAC hours.

Collection of human breath samples. End-tidal breath samples (20 ml) were collected in ground-glass syringes at 20-min intervals via a 14-gauge polyvinyl chloride tracheal catheter, the tip of which just protruded beyond the end of the endotracheal tube (measured before intubation). The catheter was thoroughly flushed with the sample before collection. The fresh gas flow was reduced to 300 ml min^{-1} and the lungs ventilated manually for precisely 1 min before sampling. The breath sample was then collected over 20 s with the bag full at apnoea. Preliminary experiments established that this technique resulted in the most reliable collection of samples as determined by the proximity of blood halothane concentration expressed as a fraction of the blood value corresponding to MAC and halothane concentration as a fraction of MAC in the gas sample obtained.

Breath samples collected before anaesthesia revealed no endogenous compounds with peaks in the vicinity of the reductive metabolites of halothane. Quantification of CDF and CTF in the breath samples was performed immediately by gas–liquid chromatography (Cousins et al., 1979).

Animal studies

Animals. Male inbred Fischer 344 rats weighing 200–250 g were housed under controlled conditions of light and temperature (Cousins et al., 1979). Fifty per cent of the rats were given daily i.p. injections of phenobarbitone sodium 75 mg kg^{-1} for 4 days to produce microsomal enzyme induction; those rats were given halothane under conditions of mild hypoxia (*vide infra*).

Breath sample collection from rats. The animals received 1% halothane either in 14% oxygen in 85% nitrogen or in 99% oxygen, for precisely 2 h. The end-expiratory halothane concentrations were monitored with a mass spectrometer via a nasopharyngeal probe. Breath samples (20 ml) were collected at 10-min intervals for 40 min and then at 20-min intervals thereafter, into ground-glass syringes (containing glass beads) using a glass multiport mask assembly (fig. 1) (Cousins et al., 1979). A 1-ml aliquot of each sample was injected into a 5730A Hewlett–Packard Gas Chromatograph with a 1-ml Hamilton gas-tight syringe. Table I shows the reproducibility of this technique using a standard gas mixture. (CDF and CTF (>99.9% pure) were obtained from PCR Chemicals, Gainsville, Florida.) Other chromatography conditions have been described previously (Cousins and Mazze, 1972; Cousins et al., 1979).

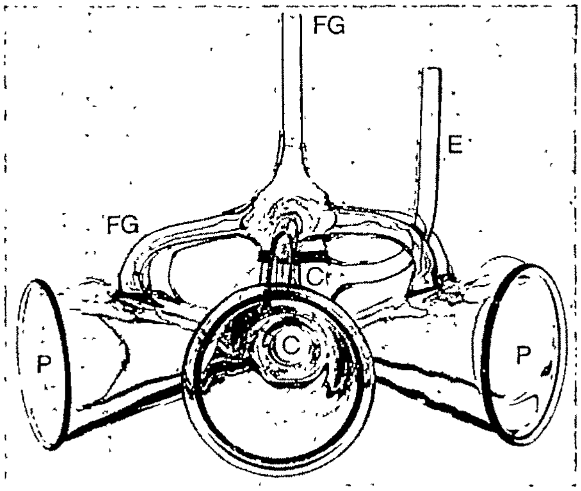


FIG. 1. Multiport rat mask assembly. Each port (P) accommodates a rat head to the level of the ears and makes a seal with a latex rubber diaphragm. The six ports are connected to a central glass chamber (C) containing soda-lime. The fresh gas supply (FG) enters above each animal head. The central exit tube (E) is used to vent excess gas and also for gas sampling. The sixth port is used for insertion of a mass spectrometer probe for continuous measurement of gaseous concentrations of halothane, oxygen and carbon dioxide.

TABLE I. *Precision of gas chromatographic method for the quantitation of CDF and CTF in gaseous samples. A standard gas mixture containing 25 p.p.m of both CDF and CTF in nitrogen was prepared. Six aliquots* (1 *ml*) *of this mixture were injected using a Hamilton gas-tight syringe into a Hewlett–Packard* 5730*A gas chromatograph as described in the methods.* **The peak area was measured using a Hewlett–Packard* 3380*A integrator and is expressed as mV* s^{-1}

	CDF (peak area)*	CTF (peak area)*
Mean	68 511	52 757
SD	535	537
Coefficient of variation (%)	0.78	1.02

Statistical analysis. The unpaired Student's *t* test was used to compare the results for variables from different experiments with a level of significance of at least $P < 0.05$.

RESULTS

Human studies

The concentration of CDF, CTF and halothane in sequential human breath samples is shown in figure 2.

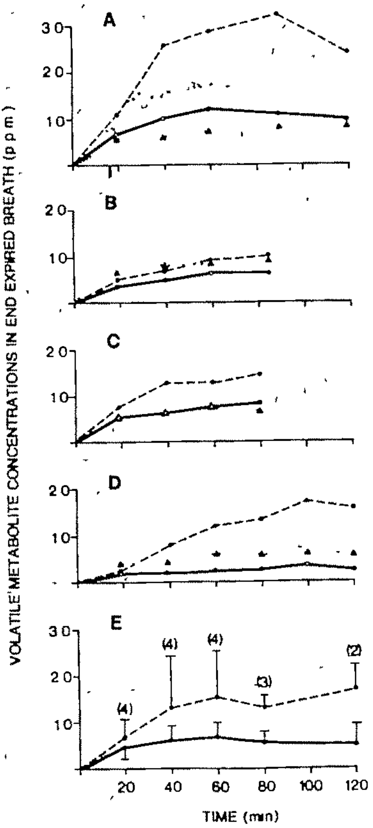


FIG. 2. Human studies: 1% halothane and 99% oxygen. The concentrations of CTF (● - - - ●), CDF (○——○) and halothane (▲...... ▲) are shown in end-expired breath samples from patients anaesthetized with halothane. The patient's steady-state halothane concentration in end-expired breath (mean ± SD of last three readings for each patient) with the various surgical procedures were: A: gastric bypass—0.81 ± 0.06%; B: hysterectomy—0.81 ± 0.02%; C: hysterectomy—0.67 ± 0.06%; D: gastric bypass—0.60 ± 0.03%. E shows the cumulative mean (± SD) of both CDF and CTF concentrations in end-expired breath at each sample time. The number in parentheses represents the number of points used during that sample period. The mean ± SD of the 60–120-min samples in E were 1.52 ± 0.34 p.p.m. (v/v) (CV = 22%) and 0.56 ± 0.1 p.p.m. (CV = 18%) for CTF and CDF respectively resulting in a CTF/CDF ratio of 2.7 : 1. The last breath sample was collected immediately before the termination of halothane administration.

It is apparent that the formation of both reductive metabolites was initiated soon after the start of the administration of halothane. The concentrations of CDF and CTF in subsequent breath samples increased with time and reached a plateau after 60 min. It should be noted that the concentrations of both CDF and CTF reported here were much greater than those reported previously by Sharp, Trudell and Cohen (1979), when sample collection occurred within 5 min of the halothane vaporizer being turned off.

A CTF/CDF ratio of 2.7 : 1 is apparent from the cumulative data (mean ± SD) from the four patients (fig. 2E).

Animal studies

The time-course of both CTF and CDF formation in the expired breath of the rats anaesthetized with 1% halothane in oxygen (fig. 3) was similar to that observed in the human studies (fig. 2). However, marked increases in the concentrations of the volatile metabolites were observed (fig. 4) when halothane (1%) was administered under conditions of mild hypoxia in the phenobarbitone-pretreated rats

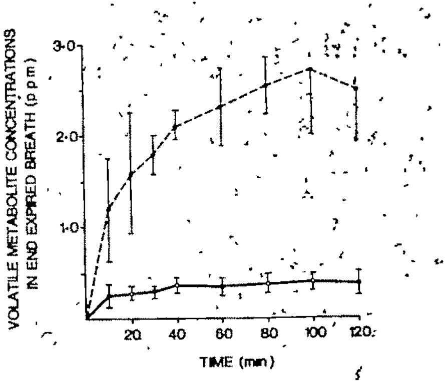


FIG. 3. Animal studies: 1% halothane and 99% oxygen. The concentrations (in p.p.m., v/v) of both CTF (● - - - ●) and CDF (○——○) are shown in end-expired breath from rats anaesthetized with 1% halothane in 99% oxygen. Fischer 344 rats were anaesthetized in groups of four and the volatile reductive metabolites collected via the glass multiport assembly as described in the Methods section. Each point in the figure represents the mean ± SD of three separate determinations using four rats in each determination. Halothane concentration in breath samples was identical to "end-expiratory concentration" obtained from continuous mass spectrometer readings of halothane via a nasopharyngeal probe. The halothane concentration in the breath samples reached a plateau by 30 min from the commencement of halothane administration. The concentration (mean ± SD) in the 30–120-min samples was 0.64 ± 0.07%.

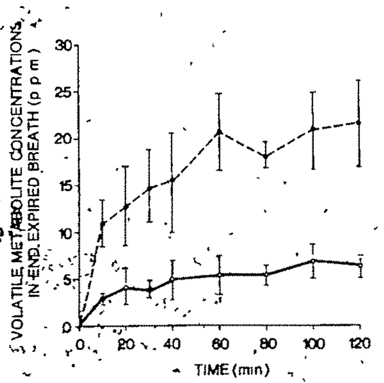


FIG. 4. Animal studies: halothane, hypoxia and enzyme induction. The concentration (in p.p.m.) of both CTF (● - - - ●) and CDF (○——○) is shown in end-expired breath from rats treated with phenobarbitone, then anaesthetized with 1% halothane in oxygen 14% in nitrogen. Fischer 344 rats were anaesthetized in groups of four and the volatile reductive metabolites collected via the glass multiport assembly. Each point in the figure represents the mean ± SD of three separate determinations using four rats in each determination. The halothane concentration in the breath samples reached a plateau by 30 min from the commencement of halothane administration. The concentration (mean ± SD) in the 30–120 min samples was 0.69 ± 0.04%.

(CDF, $P < 0.025$ for all sample times; CTF, $P < 0.01$ for all sample times). The ratio of CTF/CDF was 6.6 : 1 when halothane was administered with 99% oxygen and 3.4 : 1 with 14% oxygen and enzyme induction.

DISCUSSION

The reductive as opposed to the oxidative metabolism of halothane is assuming increasing importance in the hypothesis that reactive intermediates formed during the metabolism of halothane are responsible for the hepatic damage that sometimes follows halothane anaesthesia. The following evidence supports the role of reductive metabolism in this damage: (a) the intermediates and reductive metabolites are more reactive than the corresponding oxidative intermediates and metabolites (Widger, Gandolfi and Van Dyke, 1976); (b) spectral binding of halothane to cytochrome P_{450}, the terminal haemoprotein in the hepatic microsomal drug-metabolizing enzyme system is enhanced and modified in an anaerobic environment (Uehleke, Hellmer and Tabarelli-Poplawski, 1973); (c) covalent binding of halothane metabolites to both microsomal lipid and protein is enhanced in an hypoxic environment (Van Dyke and Gandolfi, 1974; Wood, Gandolfi and Van Dyke, 1976); and (d) marked biochemical and pathological changes have been observed in rats receiving halothane under hypoxic conditions with enzyme induction (Brown and Sipes, 1977; Cousins et al., 1979), whereas no such abnormalities are present following enzyme induction and halothane or following hypoxia and halothane.

Recently Mukai and co-workers (1977) identified two new reductive metabolites, CDF and CTF, in the breath of rabbits anaesthetized with halothane. The time-course of the formation of these two metabolites in *human breath* from the commencement of the administration of halothane (1% halothane with 99% oxygen) is provided by the present report. The concentrations of both CDF and CTF increased soon after the commencement of the administration of halothane and reached a plateau after approximately 60 min. The concentrations reported in the present communication are greater than those measured in man by Sharp, Trudell and Cohen (1979). However, in the latter report, samples were collected within 5 min of the termination of the anaesthetic. This finding suggests that the rate of formation of both CDF and CTF decreases rapidly as soon as the administration of halothane is terminated.

It is interesting that the concentrations of CTF in the obese patients were much greater than in those who were not obese, although a study of a large number of both types is necessary to confirm this finding. It is reported that the frequency of "halothane hepatitis" is greater in obese patients (Moult and Sherlock, 1975; Walton et al., 1976).

In the animal studies, which employed a model with the same route and a similar rate of halothane metabolism as man, the time-course of CDF and CTF formation was similar to that in man, in that metabolite formation began soon after the start of the administration of halothane and reached a plateau after 60 min (fig. 3). However, when the anaesthetic agent was administered to phenobarbitone-pretreated rats under hypoxic conditions, the concentrations of these reductive metabolites were increased markedly. This particular treatment regime has been shown previously (Cousins et al., 1979) to result in sharply increased serum ALT concentrations and necrotic damage in the vicinity of the central veins of the liver, resembling that observed in human liver samples from patients with halothane-associated liver damage. There is reasonable agreement between the CTF/CDF ratio of 2.7 : 1 for the patients (fig. 2E) and both 3.4 : 1 (enzyme induction and hypoxia) and 6.6 : 1 (99% oxygen) for the animal experiments.

(figs 3, 4) particularly since the tightly controlled anaesthetic conditions using non-operated rats cannot be reproduced exactly during surgery in man.

The mechanism of formation of these two reductive metabolites has been postulated (Sharp, Trudell and Cohen, 1979) to proceed through a free radical ($CF_3CHCl^{\bullet}$) and then a carbanion (CF_3CHCl^-). The reactive carbanion either eliminates a fluoride ion to form CDF or abstracts a proton from its immediate environment to produce CTF. Brown, Sipes and Baker (1977) reported central lobular necrotic damage when a solution of CTF in propylene glycol was injected directly into the portal vein of rats. This finding is in conflict with the results of Raventos and Lemon (1965) where CTF was found to be non-toxic when administered by inhalation. Therefore, it is possible that the free radical or carbanion intermediates rather than the actual metabolites CDF and CTF would initiate the cellular damage. A further reductive metabolite BCDF (2 bromo-2-chloro-1,1-difluorethylene) has been reported to be formed by reaction of halothane with hot soda-lime (Sharp, Trudell and Cohen, 1979) and possibly also by halothane reductive metabolism in man (Cohen et al., 1975). However, the amounts formed are well below toxic concentrations (Raventos and Lemon, 1965).

Although no direct relationship is proved between the two reductive metabolites (CDF and CTF) and liver damage following halothane anaesthesia, evidence is growing that reductive metabolism of halothane may be the major mechanism of "halothane hepatitis" (Cousins et al., 1978; Cousins, 1979). The measurement of breath concentrations of CDF and CTF provide a more sensitive method of estimating the extent of the reductive metabolism of halothane than the previously proposed serum fluoride determination (Widger, Gandolfi and Van Dyke, 1976).

ACKNOWLEDGEMENT

The authors would like to acknowledge the skilled technical assistance of Mr Kent Parkin.

REFERENCES

Brown, B. R., and Sipes, I. G. (1977). Biotransformation and hepatotoxicity of halothane. *Biochem. Pharmacol.*, **26**, 2091.

—— —— Baker, R. K. (1977). Halothane hepatotoxicity and the reduced derivative, 1,1,1-trifluoro-2-chloroethane. *Environ. Health Perspect.*, **21**, 185.

Cohen, E. N., Trudell, J. R., Edmunds, H. N., and Watson, E. (1975). Urinary metabolites of halothane in man. *Anesthesiology*, **43**, 392.

Cousins, M. J. (1979). Editorial: halothane and the liver. *Anaesth. Intens. Care*, **7**, 5.

—— Gourlay, G. K., Sharp, J. H., Adams, J. F., Hall, P., O'Brien, P., and Haynes, W. D. (1978). Halothane hepatitis. *Lancet*, **2**, 1197.

—— Mazze, R. I. (1972). A rapid direct injection method for determination of volatile anesthetics in whole blood. *Anesthesiology*, **36**, 293.

—— —— (1973). Methoxyflurane nephrotoxicity: a study of dose–response in man. *J.A.M.A.*, **225**, 1611.

—— Sharp, J. H., Gourlay, G. K., Adams, J. F., Haynes, W. D., and Whitehead, R. (1979). Hepatotoxicity and halothane metabolism in an animal model with application for human toxicity. *Anaesth. Intens. Care*, **7**, 9.

Moult, P. J. A., and Sherlock, S. (1975). Halothane-related hepatitis. A clinical study of twenty-six cases. *Q. J. Med.*, **44**, 99.

Mukai, S., Morio, M., Fujii, K., and Hanaki, C. (1977). Volatile metabolites of halothane in the rabbit. *Anesthesiology*, **47**, 248.

Raventos, J., and Lemon, P. G (1965). The impurities in fluothane: their biological properties. *Br. J. Anaesth.*, **37**, 716.

Sharp, J. H., Trudell, J. R., and Cohen, E. N. (1979). Volatile metabolites and decomposition products of halothane in man. *Anesthesiology*, **50**, 2.

Uehleke, H., Hellmer, K. H., and Tabarelli-Poplawski, S. (1973). Metabolic activation of halothane and its covalent binding to liver endoplasmic proteins *in vitro*. *Naunyn-Schmiedebergs Arch. Pharmacol.*, **279**, 39.

Van Dyke, R. A., and Gandolfi, A. J. (1974). Studies on irreversible binding of radioactivity from (^{14}C) halothane to rat hepatic microsomal lipids and protein. *Drug Metab. Dispos.*, **2**, 469.

Walton, B., Simpson, B. R., Strunin, L., Doniach, D., Perrin, J., and Appleyard, A. J. (1976). Unexplained hepatitis following halothane. *Br. Med. J.*, **1**, 1171.

Widger, L. A., Gandolfi, A. J., and Van Dyke, R. A. (1976). Hypoxia and halothane metabolism *in vivo*. *Anesthesiology*, **44**, 197.

Wood, C. L., Gandolfi, A. J., and Van Dyke, R. A. (1976). Lipid binding of a halothane metabolite. *Drug Metab. Dispos.*, **4**, 305.

TEMPS NECESSAIRE A LA FORMATION DES METABOLITES REDUCTEURS VOLATILS DE L'HALOTHANE CHEZ LES HUMAINS ET SUR UN MODELE ANIMAL

RESUME

Le temps nécessaire à la formation de 2-chloro-1,1,1-trifluoroéthane (CTF) et de 2-chloro-1,1-difluoroéthylène (CDF), qui sont deux métabolites réducteurs volatils de l'halothane que l'on a récemment identifiés, a fait l'objet d'études sur quatre malades auxquels on avait administré 1% d'halothane et 99% d'oxygène. Les concentrations de CTF et de CDF ont augmenté avec le temps à la fin de l'expiration et ont atteint un plateau environ 60 min après le commencement de l'administration. On a constaté une durée de temps et un plateau similaires lorsque 344 rats (Fischer) ont été anesthésiés avec 1% d'halothane dans l'oxygène. Il y a cependant eu une augmentation dans les concentrations de CTF et de CDF respectivement de

huit fois et de douze fois lorsque l'halothane (1%) a été administré dans des conditions d'hypoxie bénigne (14% d'oxygène inspiré) à des rats prétraités au phénobarbitone (ceci entraîne une augmentation marquée de l'aminotransférase de l'alanine du sérum (ALT) et des dommages nécrosiques dans le voisinage des veines se trouvant au centre du foie). On pense que les concentrations de CDF et de CTF dans la respiration constituent une méthode sensible pour la surveillance du métabolisme réducteur de l'halothane.

ZEITABLAUF DER BILDUNG FLÜCHTIGER REDUKTIVER METABOLITEN VON HALOTHAN BEI MENSCHEN UND EINEM TIERMODELL

ZUSAMMENFASSUNG

Der Zeitablauf der Bildung von 2-chloro-1,1,1-Trifluoroäthan (CTF) und 2-chloro-1,1-Difluoroäthylen (CDF), zweier vor kurzem identifizierten flüchtigen Metaboliten von Halothan, wurde bei vier Patienten studiert, die 1% Halothan mit 99% Sauerstoff erhalten hatten. Die CTF- und CDF-Konzentrationen in der Endausatmungsluft stiegen mit der Zeit an, und ein Plateau wurde beobachtet, also Fischer 344 Ratten mit 1% Halothan in Sauerstoff narkotisiert wurden. Es kam jedoch zu einem achtfachen, bezw. zwolffachen Anstieg der CTF- und CDF-Konzentrationen, wenn 1% Halothan an Ratten verabreicht wurde, die in einem milden Zustand von Hypoxie (durch 14% Sauerstoff) waren und mit Phenobarbiton vorbehandelt wurden. Dies fuhrt zu einem deutlichen Anstieg der Serum-Alaninaminotransferase (ALT) und zu nekrotischen Beschädigungen nahe den Leber-Zentralvenen. Es wird angenommen, dass die CDF- und CTF-Konzentrationen im Atem eine gute Methode zur Messung der reduktiven Halothan-Metaboliten darstellen.

PASO DEL TIEMPO DE LA FORMACION DE METABOLITOS REDUCTIVOS VOLATILES DEL HALOTANO EN SERES HUMANOS Y EN UN MODELO ANIMAL

SUMARIO

El paso del tiempo en la formación del 2-cloro-1,1,1-trifluoroetano (CTF) y del 2-cloro-1,1-difluoroetileno (CDF), dos metabolitos reductivos volatiles del halotano recién identificados, fué objeto de un estudio en cuatro pacientes a los cuales se administró un 1% de halotano con 99% de oxígeno. Las concentraciones de CTF y de CDF en el soplo terminal expirado aumentaron con el tiempo y alcanzaron un nivel estable después de aproximadamente 60 min después del comienzo de la administración. Se observó un paso del tiempo y un nivel estable similares cuando los 344 ratones de Fischer fueron anestesiados con un 1% de halotano en oxígeno. Sin embargo, hubo un aumento de ocho veces y de doce veces en las concentraciones de CTF y CDF, respectivamente cuando de administró un 1% de halotano bajo condiciones de hipoxia ligera (14% de oxígeno inspirado) a ratones que habían recibido un tratamiento previo de fenobarbitona (esto acarrea un aumento marcado de la aminotransferasa de alanina del suero (ALT) y en lesiones necróticas en los alrededores de las venas centrales del hígado). Se sugiere que las concentraciones respiratorias de CDF y de CTF suministran un método sensible de controlar el metabolismo reductivo del halotano.

Br. J. Anaesth. (1980), **52**, 337

CIRCULATORY RESPONSES OF THE DOG TO ACUTE ISOVOLUMIC ANAEMIA IN THE PRESENCE OF HIGH-GRADE ADRENERGIC BETA-RECEPTOR BLOCKADE

T. N. S. Clarke, P. Foëx, J. G. Roberts, C. A. Saner and M. J. Bennett

SUMMARY

The haemodynamic responses to isovolumic anaemia (dextran-for-blood exchange) were studied in seven dogs pretreated with propranolol 20 mg/kg body weight for 3 weeks. Adrenergic beta-receptor blockade did not prevent significant increases in heart rate (up to 19%). Cardiac output increased by about 20% while systemic vascular resistance decreased by the same proportion. Oxygen extraction increased from 24% to 35% and this was reflected by a decrease in mixed venous Po_2 by 1.2 kPa. The modest hyperdynamic response of the circulation to haemodilution in the presence of high-grade adrenergic beta-receptor blockade is in sharp contrast with the large hyperdynamic response that has been reported in its absence and indicates that normal compensatory mechanisms are considerably impaired.

Active haemodilution may be used in situations of abnormal haemoconcentration such as polycythaemia and modest haemodilution before or during operation makes it possible to minimize or avoid the transfusion of homologous blood. In addition, moderate haemodilution is used commonly when surgery requires the use of an extracorporal circulation. Since moderate haemodilution is tolerated well, it is tempting to assume that tissue perfusion remains adequate because of a decrease in blood viscosity. However, the decrease in blood viscosity is only one of the alterations in the circulation which follow active haemodilution. In response to isovolumic haemodilution the circulation becomes hyperdynamic, a response caused partly by an increase in sympathetic nervous activity (particularly noticeable at the level of the beta-adrenergic receptors), partly by arteriolar vasodilatation and by the decrease in blood viscosity (that is systemic vascular resistance and aortic input impedance decrease). The increase in beta-adrenergic activity is attested by increases in heart rate and of various indices of myocardial performance (Biro et al., 1976). The decrease in resistance to left ventricular (LV) ejection is attested by the decrease of both systemic vascular resistance and aortic input impedance (Biro et al., 1976; Clarke et al., 1978). The increase in cardiac output which follows isovolumic haemodilution anaemia may be explained easily by the decrease in impedance to left ventricular ejection occurring at a time when myocardial performance is enhanced by beta-adrenergic stimulation. This increase in cardiac output is an important factor in the maintenance of an adequate oxygen flux to the tissues but, consequently, the workload of the heart is increased. However, should coronary reserve be depleted, myocardial function may become markedly abnormal in response to haemodilution (Hagl et al., 1977).

Suppression of the effect of beta-adrenergic stimulation on the heart, by the i.v. administration of propranolol, has been shown to bring the cardiac output to the value existing before haemodilution (Clarke et al., 1978). This decreases considerably the arterial oxygen flux to the tissues. With the growing use of beta-adrenergic receptor blocking drugs in the treatment of patients suffering from cardiovascular diseases and likely to require surgery under extracorporeal circulation, the effect of prolonged beta-adrenergic blockade on the response to haemodilution has become an important issue. This is why a study of the response to isovolumic haemodilution was undertaken in dogs pretreated with propranolol.

METHODS

Seven mongrel dogs (weight 14–15 kg) were treated with oral propranolol 20 mg kg^{-1} per day for a period of 3 weeks. After 2 weeks of treatment, thoracotomy was performed. An electromagnetic flow transducer

---

T. N. S. Clarke, M.B., B.CH., D.PHIL.; P. Foëx, M.A., D.PHIL. (D.M.GENEVA); J. G. Roberts, M.B., B.S., D.PHIL., F.F.A.R.A.C.S.; C. A. Saner, B.V.SC., M.R.C.V.S., M.SC.; M. J. Bennett, B.SC.; Nuffield Department of Anaesthetics, The Radcliffe Infirmary, Oxford OX2 6HE.

0007–0912/80/030337–05 $01.00

© Macmillan Journals Ltd 1980

was implanted around the root of the aorta, a miniature pressure transducer was implanted in the cavity of the left ventricle and catheters were inserted into both the pulmonary artery and the left atrium. The surgical technique and details of the postoperative care have been described fully elsewhere (Roberts et al., 1976). During the week after operation the treatment with oral propranolol was continued and the full daily dose was given approximately 2 h before the beginning of the study. No premedication was given on the study day. Anaesthesia was induced with thiopentone 8 mg kg^{-1} and maintained with halothane 1% in nitrous oxide (50%) and oxygen (50%). The lungs were ventilated artificially at a constant rate (12 b.p.m.) and constant tidal volume (25 ml kg^{-1}). Carbon dioxide was added to the inspired gas mixture to ensure an end-tidal concentration of 5.2%. E.c.g., aortic pressure, left atrial pressure, left ventricular pressure, aortic blood flow, aortic blood acceleration, stroke volume and left ventricular dP/dt were recorded. Aortic and mixed venous blood samples were analysed for Po_2, Pco_2, pH, and haemoglobin concentration. Details of the methods have been described previously (Roberts et al., 1976; Clarke et al., 1978).

Experimental programme

Following the connection of the transducers, a period of 1 h was allowed to elapse in order to obtain a stable cardiovascular state. Each animal was subjected to a sham blood exchange initially and then to a dextran-for-blood exchange during the same study day. After haemodynamic variables had been recorded and blood samples had been taken for blood-gas analyses, blood was removed rapidly from the aortic cannula and collected in a heparinized bottle (kept at 37 °C) until the bled volume was 25–30 ml kg^{-1}. The shed blood was reinfused immediately. Five minutes later the same amount of blood was removed and then reinfused immediately. After this sham experiment, recordings were obtained after 2, 5, 10, 15, 30 and 60 min. Blood samples were taken after 15, 30 and 60 min. For the dextran-for-blood exchange, the same two-stage protocol was followed, but instead of reinfusing the shed blood, a volume of warmed 6% Dextran 70 (Pharmacia), to which supplementary electrolytes had been added to approximate the normal electrolyte composition of the dog's plasma (Fowler and Holmes, 1964) was infused. In view of the apparent hyperosmotic nature of this dextran preparation (Gold and Murray, 1969) resulting in a 15% overexpansion of the blood volume, the volume of dextran given was 15% less than the bled volume. Recordings and blood samples were obtained exactly as described above.

It must be noted that, in these dogs, a dose–response curve to isoprenaline had been constructed demonstrating a 30-fold shift to the right by comparison with the responses of untreated animals.

Computation

Systemic vascular resistance was calculated as the ratio of mean arterial pressure and cardiac output neglecting mean right atrial pressure (McDonald, 1960) and expressed in kPa $litre^{-1}$ min. From the recorded traces, six aortic blood velocity curves and six aortic pressure curves were produced manually at intervals of 12 ms, starting at the instant of aortic valve opening. The values were transferred, together with calibration constants, to punch cards. These were analysed by the ICL 1906A computer of the Oxford University Computer Centre, which was programmed to calculate the distribution of left ventricular power and work as described by Gersh and colleagues (1972).

RESULTS

The results of the sham-exchange are summarized in table I. There was no significant effect of the sham-exchange on these haemodynamic values or arterial and mixed venous blood-gas tensions obtained at 15, 30 and 60 min. There was, however, an immediate but transient effect of the sham exchange: at 2 min cardiac output was decreased by 11% and aortic blood acceleration by 10%. These alterations were significant but had disappeared by the 5th min after the sham exchange.

The results of dextran-for-blood exchange are summarized in table II. There was a decrease in haemoglobin concentration of 48% (15 min) and 50% (30 and 60 min) which was accompanied by decreases in arterial oxygen content of 45% (15 min) and 48% (60 min). Although arterial Po_2 was maintained within very narrow limits during the exchange procedure, mixed venous Po_2 was decreased significantly by 0.9 kPa at 15 min, 1.1 kPa at 30 min and 1.2 kPa at 60 min. Thus, mixed venous oxygen content decreased more than arterial oxygen content and was reduced by 52% (15 min) and 56% (30 and 60 min). The arterial to mixed venous oxygen content difference was decreased by approximately 26% after the dextran-for-blood exchange. In response to haemodilution with dextran, heart rate

TABLE I. *Effect of sham isovolumic blood exchange on the circulation and on blood-gases in seven dogs pretreated with propranolol. Mean ± SEM of seven experiments*

	Control	Time after sham-exchange		
		15 min	30 min	60 min
Heart rate (beat min^{-1})	109±5	108±5	107±5	109±5
Mean arterial pressure (mm Hg)	78±8	79±7	78±7	78±8
Stroke volume (ml kg^{-1})	1.51±0.13	1.53±0.15	1.51±0.13	1.48±0.13
Cardiac output (ml min^{-1} kg^{-1})	165±14	164±14	161±12	159±11
Systemic vascular resistance (kPa $litre^{-1}$ min)	4.78±0.62	4.97±0.72	4.90±0.70	4.93±0.73
LVEDP (mm Hg)	5±1.9	4±1.5	5±1.5	6±1.5
Peak aortic blood acceleration (ml s^{-2})	5760±740	5660±820	5750±740	5640±680
LV dP/dt max (mm Hg s^{-1})	1850±150	1890±160	1870±170	1860±175
LV dP/dt max/IP (s^{-1})	38±3.4	38±3.8	38±3.0	37±3.4
Peak LV power (mW)	2522±283	2552±258	—	2522±254
LV stroke work (mJ)	304±115	309±32	—	299±31
Pa_{O_2} (kPa)	27.8±2.4	27.7±2.3	27.2±2.4	27.7±2.4
Pa_{CO_2} (kPa)	5.7±0.3	5.9±0.2	5.7±0.2	5.7±0.3
pHa	7.34±0.01	7.34±0.02	7.34±0.02	7.34±0.01
$P\bar{v}_{O_2}$ (kPa)	6.4±0.4	6.7±0.5	6.5±0.5	6.8±0.4
$P\bar{v}_{CO_2}$ (kPa)	6.7±0.3	6.7±0.3	6.5±0.4	6.5±0.4
pH$\bar{v}$	7.32±0.01	7.32±0.01	7.31±0.02	7.32±0.02
Ca_{O_2} (ml dl^{-1})	13.7±0.6	13.4±0.5	12.3±0.5	13.0±0.3
$C\bar{v}_{O_2}$ (ml dl^{-1})	10.0±0.6	9.9±0.5	9.0±0.5	9.9±0.4
($Ca_{O_2}-C\bar{v}_{O_2}$) (ml dl^{-1})	3.7±0.4	3.5±0.5	3.3±0.5	3.1±0.3
Hb (g dl^{-1})	9.9±0.5	9.6±0.3	8.6±0.4	9.3±0.2

TABLE II. *Effect of dextran-exchange isovolumic anaemia on the circulation and on blood-gases in seven dogs pretreated with propranolol. Mean ± SEM of seven experiments. Symbols for statistical significance (paired two-tailed Student's* t *tests)* $^*P<0.05$; $^{**}P<0.005$

	Control	Time after dextran-exchange		
		15 min	30 min	60 min
Heart rate (beat min^{-1})	108±5	117±4*	122±4*	128±8*
Mean arterial pressure (mm Hg)	78±8	81±5	76±3	78±6
Stroke volume (ml kg^{-1})	1.49±0.14	1.58±0.16	1.58±0.14	1.57±0.14
Cardiac output (ml min^{-1} kg^{-1})	159±13	185±20	194±20	202±23
Systemic vascular resistance (kPa $litre^{-1}$ min)	5.02±0.80	4.52±0.52	4.13±0.42	3.88±0.30
LVEDP (mm Hg)	5±1.1	8±1.5*	8±1.5*	6±1.1
Peak aortic blood acceleration (ml s^{-2})	5650±710	5735±800	5870±770	6120±875
LV dP/dt max (mm Hg s^{-1})	1830±175	1965±250	2060±240	2080±230*
LV dP/dt max/IP (s^{-1})	38±3.4	40±4.5	40±4.5	39±3.4
Peak LV power (mW)	2550±265	2550±310	—	2750±385
LV stroke work (mJ)	287±30	322±38	—	332±44
Pa_{O_2} (kPa)	27.8±0.9	28.0±0.8	28.3±0.9	28.7±1.0
Pa_{CO_2} (kPa)	5.6±0.1	5.9±0.1	5.6±0.1	5.6±0.1
pHa	7.34±0.01	7.34±0.02	7.33±0.02	7.34±0.01
$P\bar{v}_{O_2}$ (kPa)	6.8±0.4	5.9±0.1*	5.7±0.01**	5.6±0.1**
$P\bar{v}_{CO_2}$ (kPa)	6.5±0.2	6.5±0.2	6.5±0.2	6.3±0.1
pH$\bar{v}$	7.32±0.02	7.31±0.02	7.31±0.02	7.32±0.02
Ca_{O_2} (ml dl^{-1})	13.0±0.3	7.1±0.3**	6.7±0.5**	6.8±0.3**
$C\bar{v}_{O_2}$ (ml dl^{-1})	9.9±0.4	4.8±0.3**	4.4±0.4**	4.4±0.3**
($Ca_{O_2}-C\bar{v}_{O_2}$) (ml dl^{-1})	3.1±0.3	2.3±0.1**	2.4±0.2**	2.4±0.1**
Hb (g dl^{-1})	9.3±0.2	4.8±0.2**	4.6±0.4**	4.6±0.3**

increased significantly by 8% (15 min), 13% (30 min) and 19% (60 min). Stroke volume increased slightly (+5.5%), but not significantly. Cardiac output increased by 16%, 22% and 27% at 15, 30 and 60 min respectively. However, because of the greater scatter, these changes were not statistically significant. Systemic vascular resistance decreased by 10%, 18% and 23% at 15, 30 and 60 min respectively. Indices of myocardial performance increased by between 8 and 13%. The 13% increase of LV d*P*/d*t* max observed 60 min after exchange was statistically significant.

DISCUSSION

The induction of an acute isovolumic dextran-exchange anaemia in the dog is known to cause an increase in cardiac output and a decrease in systemic vascular resistance (Fowler, Franch and Bloom, 1956; Lovegrove, Gowdey and Stevenson, 1957; Richardson and Guyton, 1959; Escobar et al., 1966; Murray and Escobar, 1968; Biro et al., 1976; Clarke et al., 1978). Stimulation of the beta-adrenergic receptors appears to be an important determinant of the response to isovolumic anaemia; this is confirmed by observations of substantial increases of heart rate and of myocardial performance (Biro et al., 1976; Clarke et al., 1978). Although beta-adrenergic receptor stimulation is present, infusions of isoprenaline may cause further increases of heart rate and of myocardial performance (Biro et al., 1976).

Blockade of beta-adrenergic receptors with i.v. propranolol has been shown to suppress the hyperdynamic response of the circulation to isovolumic anaemia (Clarke et al., 1978). That cardiac output returned to values identical to those observed before haemodilution, although vascular resistance remained decreased, suggests a decrease in myocardial performance after beta-adrenergic receptor blockade with propranolol i.v. The observed reduction of left ventricular peak power may be indicative of impaired contractility.

In the present study, very large doses of oral propranolol were administered sufficient to cause a 30-fold shift to the right of the isoprenaline dose–response curve (Roberts et al., 1976). Such a high degree of blockade of the adrenergic beta-receptors did not prevent significant increases in heart rate, of a magnitude comparable to that observed in the absence of blockade of these receptors (Clarke et al., 1978). The likely explanation for the increases in heart rate was a decrease in vagal tone, since the chronotropic effects of adrenergic stimulation were blocked. Pretreatment with propranolol, however, prevented the development of a marked hyperdynamic response of the circulation to haemodilution. The increase in cardiac output, essentially a result of the increase in heart rate, was only 22% while, in the absence of blockade of the adrenergic beta-receptors, increases of 64% could be expected (Biro et al., 1976). Modest increases of indices of myocardial performance could be attributed to alterations in heart rate, preload and afterload rather than to increases of pure contractility, since the inotropic effect of adrenergic stimulation was blocked. Significant and large increases (about 40%) could be expected in the absence of adrenergic beta-receptor blockade (Biro et al., 1976). One effect of haemodilution is to decrease blood viscosity. In this study, vascular resistance was decreased by about 23%, but the experimental design did not allow for separating arteriolar vasodilatation and reduction of blood viscosity. The absence of haemodynamic changes after the sham exchange indicated that haemodilution, and not the transient period of hypovolaemia which accompanied withdrawal of blood, was responsible for these alterations.

Oxygen availability may be maintained at an acceptable level in the case of haemodilution anaemia by an increase in cardiac output or by an increase in the extraction of oxygen at the tissue level. The latter was observed in this study: mixed venous $P\text{O}_2$ decreased significantly by up to 1.2 kPa, confirming that oxygen extraction had increased from 24% to 35%. At the same time, although a high degree of blockade of the adrenergic beta-receptors was present, the circulation was moderately hyperdynamic. The lesser degree of hyperdynamic compensation for the decrease in arterial oxygen content may indicate that not much reserve was left and that increases in oxygen tissue requirements could not be met. On the other hand, if the hyperdynamic response of the circulation is minimized, myocardial oxygen requirements are maintained within normal limits and are not increased greatly. Therefore, the balance between oxygen supply and demand is protected.

In the face of blockade of the adrenergic beta-receptors, the hyperdynamic response of the circulation to isovolumic haemodilution is minimized without being suppressed; oxygen availability to the tissues is decreased more than in the absence of blockade. However, myocardial oxygen requirements are increased less and thus the risks of imbalance between supply and demand may be minimized.

ACKNOWLEDGEMENTS

We are indebted to Mr W. A. Ryder, Mr J. Aspel, Mr P. Maynard and Mr R. Restall for their skilled technical assistance. T. N. S. Clarke was in receipt of a Medical Research Council Scholarship for training in research methods. C. A. Saner was in receipt of a Rhodes Scholarship.

REFERENCES

Biro, G. P., Foex, P., Clarke, T. N. S., and Prys-Roberts, C. (1976). Cardiac responsiveness to beta-adrenergic stimulation in experimental anaemia. *Can. J. Physiol. Pharmacol.*, **54**, 675.

Clarke, T. N. S., Prys-Roberts, C., Biro, G. B., Foex, P., and Bennett, M. J. (1978). Aortic input impedance and left ventricular energetics in acute isovolumic anaemia. *Cardiovasc. Res.*, **12**, 49.

Escobar, E., Jones, N. L., Rapaport, E., and Murray, J. F. (1966). Ventricular performance in acute normovolemic anemia and effects of beta-blockade. *Am. J. Physiol.*, **211**, 877.

Fowler, N. O., Franch, R. H., and Bloom, W. L. (1956). Hemodynamic effects of anemia with and without plasma volume expansion. *Circ. Res.*, **4**, 319.

—— Holmes, J. C. (1964). Dextran exchange anemia and reduction in blood viscosity in the heart–lung preparation. *Am. Heart J.*, **68**, 204.

Gersh, B. J., Prys-Roberts, C., Reuben, S. R., and Schultz, D. L. (1972). The effects of halothane on the interaction between myocardial contractility, aortic input impedance and left ventricular performance. II: Aortic input impedance and the distribution of energy during ventricular ejection. *Br. J. Anaesth.*, **44**, 767.

Gold, P. M., and Murray, J. F. (1969). Changes in red cell distribution, hemodynamics and blood volume in acute anemia. *J. Appl. Physiol.*, **26**, 589.

Hagl, S., Heimisch, W., Meisner, H., Erben, R., Baum, M., and Mendler, N. (1977). The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Res. Cardiol.*, **72**, 344.

Lovegrove, T. D., Gowdey, C. W., and Stevenson, J. A. F. (1957). Sympathoadrenal system and response of heart to acute exchange anemia. *Circ. Res.*, **5**, 659.

McDonald, D. A. (1960). *Blood Flow in Arteries.* London: Arnold.

Murray, J. F., and Escobar, E. (1968). Circulatory effects of blood viscosity: comparison of methemoglobinemia and anemia. *J. Appl. Physiol.*, **25**, 594.

Richardson, T. Q., and Guyton, A. C. (1959). Effects of polycythemia and anemia on cardiac output and other circulatory factors. *Am. J. Physiol.*, **197**, 1167.

Roberts, J. G., Foëx, P., Clarke, T. N. S., and Bennett, M. J. (1976). Haemodynamic interactions of high-dose propranolol pretreatment and anaesthesia in the dog. I: Halothane dose–response studies. *Br. J. Anaesth.*, **48**, 315.

REACTIONS CIRCULATOIRES DU CHIEN A L'ANEMIE ISOVOLUMIQUE AIGUE EN PRESENCE D'UN FORT BLOCAGE ADRENERGIQUE DU RECEPTEUR BETA

RESUME

On a étudié pendant 3 semaines sur sept chiens prétraités au propranolol (à raison de 20 mg kg^{-1} de poids du corps) les réactions hémodynamiques à l'anémie isovolumique (échange dextrane/sang). Le blocage adrénergique du récepteur béta n'a pas empêché une augmentation sensible de la fréquence cardiaque (jusqu'à 19%). Le débit cardiaque a augmenté d'environ 20% alors que la résistance vasculaire systémique a diminué dans les mêmes proportions. L'extraction d'oxygène est passée de 24% à 35% et ceci s'est reflété par une diminution d'environ 1,2 kPa de la $P\text{O}_2$ veineuse mixte. La réaction hyperdynamique modeste de la circulation à l'hémodilution en présence d'un fort blocage adrénergique du récepteur béta est en contraste marqué à la réaction hyperdynamique importante que l'on a signalée en son absence et indique que les mécanismes compensatoires normaux sont considérablement altérées.

KREISLAUFREAKTIONEN BEIM HUND AUF ISOVOLUMISCHE ANÄMIE IN ANWESENHEIT EINER HOCHGRADIGEN ADRENERGISCHEN BETA-REZEPTOR-BLOCKIERUNG

ZUSAMMENFASSUNG

Die hämodynamischen Reaktionen auf isovolumische Anämie (Dextran-für-Blut-Austausch) wurden bei 7 Hunden studiert, die 3 Wochen lang mit 20 mg/kg Körpergewicht vorbehandelt wurden. Die adrenergische Beta-Rezeptor-Blockierung verhinderte nicht deutliche Steigerungen der Herztätigkeit (bis zu 19%). Das Herzminutenvolumen stieg um etwa 20%, während der systemische Gefasswiderstand im selben Verhältnis sank. Sauerstoffentnahme stieg von 24% auf 35%, was sich durch einen Abstieg der gemischten venösen $P\text{O}_2$ um 1,2 kPa zeigte. Die geringe hyperdynamische Reaktion des Kreislaufs auf Hämodilution in Anwesenheit einer hochgradigen adrenergischen Beta-Rezeptor-Blockierung steht in scharfem Gegensatz zu der starken hyperdynamischen Reaktion in deren Abwesenheit, und zeigt, dass die normalen Ausgleichsmechanismen stark beeinträchtigt sind.

RESPUESTAS CIRCULATORIAS DEL PERRO A UNA ANEMIA ISOVOLUMICA AGUDA EN PRESENCIA DE UN BLOQUE BETA-RECEPTOR ADRENERGICO DE ALTO GRADO

SUMARIO

Se realizó un estudio de las respuestas hemodinámicas a la anemia isovolúmica (intercambio dextrán/sangre) en siete perros tratados previamente con 20 mg kg^{-1} peso corporal de propranolol durante 3 semanas. El bloqueo beta-receptor adrenérgico no impidió aumentos significativos del ritmo cárdiaco (hasta un 19%). El volumen-minuto creció en approximadamente 20% mientras que la resistencia vascular sistémica disminuía en la misma proporción. La extracción de oxígeno se incrementó de un 24% a un 35% y esto se reflejó en un descenso de 1,2 kPa del $P\text{O}_2$ venoso mixto. La respuesta hiperdinámica moderada de la circulación a la hemodilución en presencia de un bloqueo beta-receptor adrenérgico de alto grado contrasta mucho con la importante respuesta hiperdinámica registrada en ausencia del mismo e indica que los mecanismos compensatorios normales se hallan considerablemente afectados.

Br. J. Anaesth. (1980), **52**, 343

EFFECT OF ANAESTHESIA WITH NITROUS OXIDE IN OXYGEN AND FENTANYL ON RENAL FUNCTION IN THE ARTIFICIALLY VENTILATED DOG

J. M. Hunter, R. S. Jones and J. E. Utting

SUMMARY

The effect on renal function of a large dose (25 μg kg^{-1}) of fentanyl was investigated in 10 labrador dogs. The animals were anaesthetized with nitrous oxide in oxygen and a small supplement of fentanyl 0.4 μg min^{-1} throughout the experiment, and muscular relaxation was provided by alcuronium, pulmonary ventilation being controlled. In the initial phase of each experiment, estimated renal plasma flow, glomerular filtration rate, urine volume, mean arterial pressure and renal vascular resistance were measured at 30-min intervals, three sets of samples being taken. Then the large dose of fentanyl was given over a 10-min period and the measurements were repeated at 30-min intervals for 90 min. Changes in renal function lasted for about 90 min; there was a significant decrease in estimated renal plasma flow ($P < 0.01$), glomerular filtration rate ($P < 0.001$), urine volume ($P < 0.01$) and mean arterial pressure ($P < 0.001$) together with an increase in renal vascular resistance ($0.05 > P > 0.02$). These changes were accompanied by bradycardia, but were still present when atropine was given.

The effect of a small dose of the potent analgesic fentanyl on renal function has been found to be slight, both in the human subject (Gorman and Craythorne, 1966) and in the dog (Hunter et al., 1979).

Hunter and colleagues (1979) investigated the use of a small dose of fentanyl as an adjuvant to anaesthesia with nitrous oxide and oxygen in paralysed dogs, when pulmonary ventilation was controlled. They concluded that renal blood flow, for example, was little different from that considered normal in conscious dogs.

More significantly, Bidwai and colleagues (1976) studied the effect of very large doses of fentanyl on renal function in the dog anaesthetized with intermittent thiopentone and subjected to artificial pulmonary ventilation with 100% oxygen, muscular relaxation being provided by intermittent suxamethonium. They gave a constant i.v. infusion of fentanyl at the rate of 10 μg kg^{-1} min^{-1} and measured urine volume (V), estimated renal plasma flow (ERPF) and glomerular filtration rate (GFR) at regular intervals. They found that, although there was a decrease in mean arterial pressure and urine production during anaesthesia, there was no significant change in ERPF or GFR from control values obtained before induction, despite the use of what, by clinical standards, are extremely large doses of fentanyl (up to 1000 μg kg^{-1} given over 100 min).

This paper describes the effect on renal function of a large dose (25 μg kg^{-1}) of fentanyl administered over a period of 10 min to dogs already anaesthetized with nitrous oxide and oxygen supplemented with a very small constant infusion of fentanyl 0.4 μg min^{-1} to maintain adequate anaesthesia.

METHODS

Ten labrador dogs (average weight 20 kg) were starved overnight and no premedication was given. Anaesthesia was induced with thiopentone 300 mg given with fentanyl 5 μg kg^{-1} and atropine 0.6 mg i.v. Following endotracheal intubation alcuronium 2.5 mg was given and intermittent positive pressure ventilation with nitrous oxide 67% in oxygen was commenced, using a Mapleson E type circuit and a Beaver ventilator (Lamplugh, Jones and Snowdon, 1979). Further increments of alcuronium 2.5 mg were given as required throughout the experiment to maintain muscle relaxation. Normocapnia (5–5.5 kPa) was maintained throughout by adjusting the fresh gas flow according to the arterial carbon dioxide tension; this was measured at regular intervals using an IL blood-gas analyser (IL 213–227).

The procedures for preparing the animal and the monitoring were similar to that reported in a previous

---

J. M. Hunter, M.B., CH.B., F.F.A.R.C.S.; R. S. Jones, M.V.SC., M.R.C.V.S., D.V.A.; J. E. Utting, M.A., M.B., F.F.A.R.C.S.; University Department of Anaesthesia, Royal Liverpool Hospital, Prescot Street, P.O. Box 147, Liverpool L69 3BX.

0007-0912/80/030343-06 $01.00

© Macmillan Journals Ltd 1980

investigation of renal function under anaesthesia (Hunter et al., 1979).

Monitoring

A peripheral artery was cannulated and a venous line inserted through the recurrent tarsal vein (of the hindlimb) into the inferior vena cava (IVC). The position of this catheter was not confirmed radiologically. Arterial and venous pressure were measured directly using suitable pressure transducers (Bell and Howell type 4/327/L221) and a suitable recorder (Devices MX2R). The arterial cannula was used for blood sampling. Through the venous line in the IVC an i.v. infusion of hypotonic saline 0.45% was commenced to promote a diuresis. A separate peripheral vein was cannulated for autotransfusion of blood to maintain circulating volume during the experiment by replacing the amount used during sampling. This blood was withdrawn at least 1 week before the experiment, and stored in acid–citrate–dextrose solution in a refrigerator at 4 °C; it was not filtered or warmed before re-transfusion. The urinary bladder was catheterized.

Determination of GFR and RBF

ERPF was measured by estimating the renal clearance of para-aminohippuric acid (PAH) and GFR by estimating the renal clearance of inulin. Values for ERPF and GFR could then be obtained using the formula for renal clearance.

Once a flow of urine had been established, a loading dose of para-aminohippuric acid (PAH) 10 mg kg^{-1} and inulin 60 mg kg^{-1} was given i.v. over a 10-min period. A maintenance infusion of saline 0.45% containing inulin 5.0 mg ml^{-1}, PAH 2.5 mg ml^{-1} and a small concentration of fentanyl (0.2 μg ml^{-1}) was then started at the rate of 2 ml min^{-1}. A constant infusion pump (Watson–Marlow, Mark 3) was used for this purpose.

One hour after the loading dose had been given, the first set of samples of arterial blood and urine were collected for estimation of PAH and inulin. PAH was determined according to the method described by Dick and Davies (1949) and inulin determined according to the method described by Bacon and Bell (1947), using a double-beam spectrophotometer (Shimadsu UV 140). Urine production ($\dot{V}$) was measured (ml min^{-1}) over a 5-min period so that ERPF and GFR could be derived.

Two further sets of samples were taken at intervals of 30 min for estimation of ERPF and GFR. A large dose of fentanyl (25 μg kg^{-1}) was then given over a 10-min period, the maintenance infusion containing fentanyl, PAH and inulin being continued throughout. In three of the experiments atropine 1.2 mg was given immediately before the large dose of fentanyl. Three further sets of blood and urine samples were then taken, again at 30-min intervals, for further estimation of ERPF and GFR. Blood-gases and haematocrit (Hct) were also measured at each sampling time.

Renal blood flow (RBF) was derived using the formula:

$$\text{RBF} = \text{ERPF} \times \frac{100}{100 - \text{Hct}}$$

and renal vascular resistance (RVR) using the formula:

$$\text{RVR} = \frac{\text{Mean arterial pressure} - \text{mean venous pressure}}{\text{RBF}}$$

and finally standardized by being expressed as resistance per 100 g kidney weight where the weight of the kidney was taken as 0.3% total body weight (Gans and Mercer, 1977).

RESULTS

Cardiovascular parameters

The arterial pressure in the first part of the experiment was within the range of normal for dogs anaesthetized with pentobarbitone or sodium barbitone (Altman and Dittmer, 1964). The administration of the large dose of fentanyl, however, produced a sudden decrease in arterial pressure (fig. 1); this was

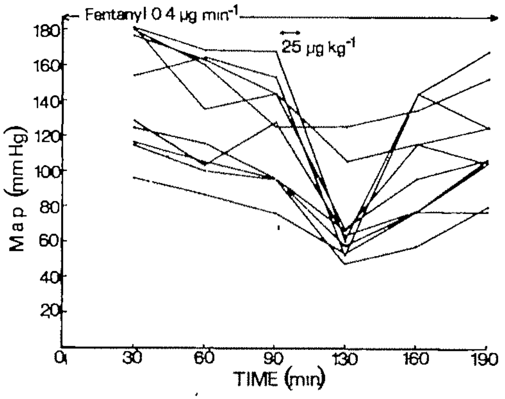


FIG. 1. The effect of a large dose of fentanyl (25 μg kg^{-1}) given over a 10-min period on mean arterial pressure. Each line represents the values obtained in one of the 10 experiments.

accompanied by a decrease in heart rate (fig. 2) except in the three experiments in which i.v. atropine was given immediately before the large dose of fentanyl, when no significant decrease in heart rate occurred.

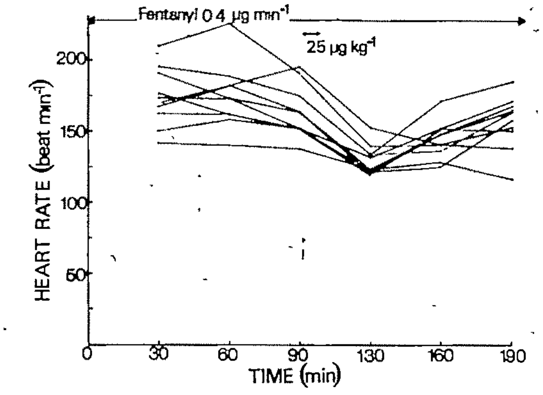


FIG. 2. The effect of a large dose of fentanyl (25 µg kg^{-1}) given over a 10-min period on heart rate in each of the 10 experiments.

Renal parameters

Following the administration of the large dose of fentanyl, there was a decrease in ERPF to a mean of 37% of the mean value obtained whilst the small dose of fentanyl was being given (fig. 3). A decrease in GFR (fig. 4) and V (fig. 5) also occurred. This was accompanied by an increase in RVR (fig. 6).

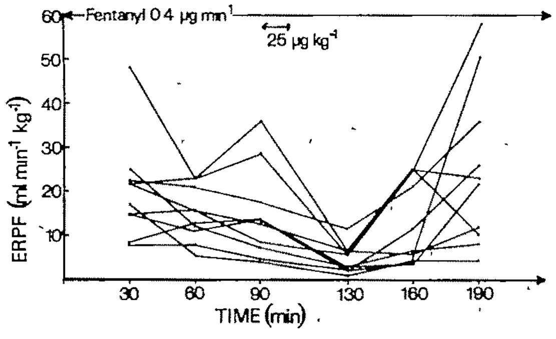


FIG. 3. The effect of a large dose of fentanyl (25 µg kg^{-1}) on estimated renal plasma flow in each of the 10 experiments.

The effects of the large dose of fentanyl were short-lived: within 90 min the variables had returned to those values found during the control period when only a small dose of fentanyl was being given.

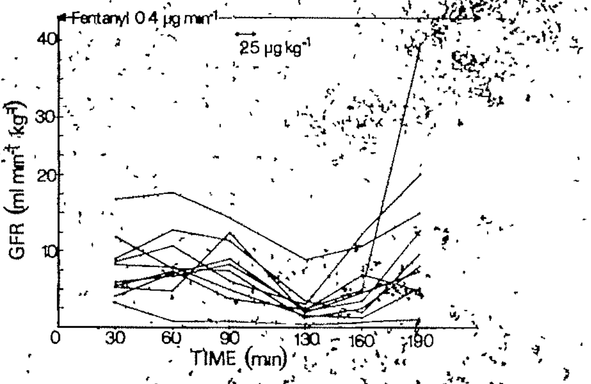


FIG. 4. The effect of a large dose of fentanyl (25 µg kg^{-1}) on glomerular filtration rate in each of the 10 experiments.

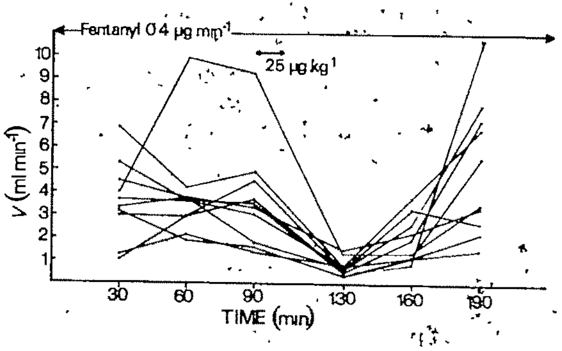


FIG. 5. The effect of a large dose of fentanyl (25 µg kg^{-1}) on urine production (V) in each of the 10 experiments.

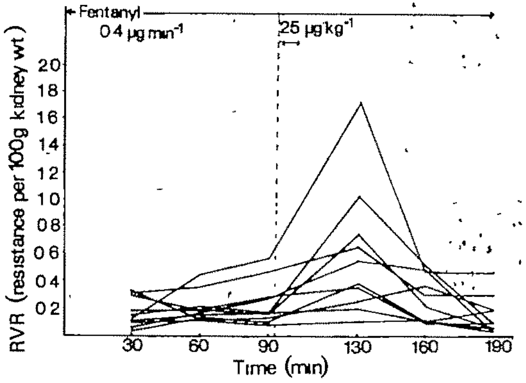


FIG. 6. The effect of a large dose of fentanyl (25 µg kg^{-1}) on renal vascular resistance per 100 g kidney weight in each of the 10 experiments.

The mean values for ERPF, GFR, RVR, V and m.a.p. immediately before and 30 min after the large dose of fentanyl are given in table I. Values for the standard deviation and standard error of the mean of these values are also given. The difference between

TABLE I. *Mean values for ERPF, GFR, RVR,* V *and m.a.p. immediately before and* 30 *min after a large dose of fentanyl* (25 $\mu g\ kg^{-1}$). *Values for the standard error of the mean* (*SEM*) *and standard deviation are also given. Significance values for the change in each variable following fentanyl* 25 $\mu g\ kg^{-1}$ *are denoted by the asterisks* $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

	ERPF (ml min^{-1} kg^{-1})	GFR (ml min^{-1} kg^{-1})	RVR (resistance per 100 g kidney)	V (ml min^{-1})	M.a.p. (mm Hg)
Before fentanyl					
Mean	14.7	7.8	0.23	3.7	134
SEM	3.2	1.3	0.05	0.7	6.6
SD	10.25	4.2	0.16	2.3	20.8
After fentanyl					
Mean	4.6**	2.6***	0.61*	0.7**	102***
SEM	1.0	0.75	0.13	0.1	2.6
SD	3.2	2.4	0.48	0.4	8.2

each of the variables immediately before and 30 min after the large dose of fentanyl was statistically significant, using the paired t test. The probability values obtained are also given in table I.

DISCUSSION

These results show that the effect of a large dose of fentanyl on renal function in the dog is greater than has been reported previously. For example, although comparison with other techniques is difficult, it can be seen that the decrease in ERPF following the large dose of the drug was much greater than the decrease in ERPF reported by Deutsch and colleagues (1966) as occurring in human volunteers spontaneously breathing nitrous oxide, oxygen and halothane (1.5%).

The renal changes induced by a large dose of fentanyl were short-lived (30–60 min). Such changes are probably not important in the healthy, well-hydrated animal or patient, but they might be in, for example, hypovolaemia. Certainly the results obtained suggest that a large dose of fentanyl will not protect the kidneys from any deterioration in function when the circulating volume is reduced.

A decrease in arterial pressure accompanied by bradycardia has been described previously after the administration of fentanyl, both in humans (Gorman and Craythorne, 1966; Marta, Davis and Eisele, 1973) and in dogs (Glen, 1970; Bidwai et al., 1976). The decreases previously reported, however, were much less than those reported here.

It is not known if the reduction is a result of a decrease in cardiac output or of a decrease in peripheral resistance, or a combination of these; for example, cardiac output might decrease and peripheral resistance might increase. Unfortunately, venous pressure changes, which might have given a clue, were small and equivocal.

It might be speculated that the primary change was a decrease in cardiac output and that the observed increase in renal vascular resistance was a result of a compensatory increase in peripheral sympathetic tone which would, of course, involve the kidney.

The reason for there being such considerable changes in renal function after a large dose of fentanyl in these experiments compared with the minimal effect found with an even greater dose by Bidwai and others (1976) is not immediately obvious. In our experiments, the amount of fentanyl given per unit time (2.5 $\mu g\ kg^{-1}\ min^{-1}$) was less than the amount given per unit time by Bidwai and colleagues (10 $\mu g\ kg^{-1}\ min^{-1}$) and would therefore have been expected to produce a less marked effect on renal function.

The values for ERPF, GFR and V obtained during the administration of a small dose of fentanyl are comparable with those found in previous work on renal function in the normocapnic, lightly anaesthetized dog (Hunter et al., 1979) and with those reported by Houck (1948) in the conscious dog. This would suggest that such small doses have minimal effect on renal function. It would appear, however, that large doses can have a considerable effect on renal function in the dog and it is possible that this occurs in man also.

ACKNOWLEDGEMENTS

This work was supported partly by Janssen Pharmaceuticals and partly by the research fund of the Mersey Regional Health Authority. The authors wish to acknowledge the encouragement given by Dr R. Cookson of Janssen Pharmaceuticals to perform these experiments, and the expert technical assistance of Miss Christina Mann.

REFERENCES

Altman, P. L., and Dittmer, D. S. (1964). *Biology Data Book*, p. 239. Washington D.C.: Federation of American Societies for Experimental Biology.

Bacon, J. S. D., and Bell, D. J. (1947). Fructose and glucose in the blood of fetal sheep. *Biochem. J.*, **42**, 397.

Bidwai, A. V., Liu, W. S., Stanley, T. H., Bidwai, V., Loeser, E. A., and Shaw, C. L. (1976). The effects of large doses of fentanyl and fentanyl with nitrous oxide on renal function in the dog. *Can. Anaesth. Soc. J.*, **23**, 296.

Deutsch, S., Goldberg, M., Stephen, G. W., and Wu, W. H. (1966). Effects of halothane anesthesia on renal function in normal man. *Anesthesiology*, **27**, 793.

Dick, A., and Davies, E. C. (1949). Measurement of the glomerular filtration rate and the effective renal plasma flow using sodium thiosulphate and para-aminohippuric acid. *J. Clin. Pathol.*, **2**, 67.

Gans, J. H., and Mercer, P. F. (1977). The kidneys; in *Dukes' Physiology of Domestic Animals* (ed. M. J. Swenson), 9th edn, p. 463. Ithaca and London: Cornell University Press.

Glen, J. B. (1970). Neuroleptanalgesia with "Thalamonal Vet" in the dog. *Proc. Assoc. Vet. Anaesth.*, **1**, 38.

Gorman, H. M., and Craythorne, N. W. B. (1966). The effects of a new neuroleptanalgesic agent (Innovar) on renal function in man. *Acta Anaesthesiol. Scand.* (Suppl.), **24**, 111.

Houck, C. R. (1948). Statistical analysis of filtration rate and effective renal plasma flow related to weight and surface area in dogs. *Am. J. Physiol.*, **153**, 169.

Hunter, J. M., Jones, R. S., Lamplugh, G., and Utting, J. E. (1979). The effect of hypocapnia on some aspects of renal function in the anaesthetized dog. *Br. J. Anaesth.*, **51**, 725.

Lamplugh, G., Jones, R. S., and Snowdon, S. L. (1979). The Mapleson E circuit and controlled ventilation using an air piston in dogs. *J. Small Anim. Pract.*, **20**, 557.

Marta, J. A., Davis, H. S., and Eisele, J. H. (1973). Vagomimetic effects of morphine and Innovar in man. *Anesth. Analg.* (*Cleve.*), **52**, 817.

EFFETS DE L'ANESTHESIE AU PROTOXYDE D'AZOTE DANS L'OXYGENE ET AU FENTANYL SUR LA FONCTION RENALE D'UN CHIEN VENTILE ARTIFICIELLEMENT

RESUME

On a étudié les effets d'une forte dose de fentanyl (25 μg kg^{-1}) sur la fonction rénale de 10 chiens Labrador. Les animaux avaient été anesthésiés au protoxyde d'azote dans l'oxygène, auquel on avait ajouté un petit supplément de fentanyl (0,4 μg min^{-1}) pendant toute la durée de l'expérience, alors que la relaxation musculaire était assurée par de l'alcuronium et la ventilation pulmonaire était effectuée sous contrôle. Au cours de la phase initiale de chaque expérience, le débit de plasma rénal estimé, le taux de filtration glomérulaire, le volume d'urine, la pression artérielle moyenne et la résistance vasculaire rénale ont été mesurés à des intervalles de 30 min, trois séries d'échantillons étant prélevées. On a ensuite administré la forte dose de fentanyl pendant une durée de 10 min et on a repris les mesures à 30-min d'intervalles, pendant 90 autres min. Les variations dans la fonction rénale ont duré pendant environ 90 min; il y a eu une diminution notoire du débit de plasma rénal estimé ($P < 0{,}01$), du taux de filtration glomérulaire ($P < 0{,}001$), du volume d'urine ($P < 0{,}01$) et de la pression artérielle moyenne ($P < 0{,}001$) de même qu'une augmentation de la résistance vasculaire rénale ($0{,}05 > P > 0{,}02$). Ces variations ont été accompagnées de bradycardie, et celle-ci était toujours présente lorsqu'on a administré l'atropine.

NARKOSEWIRKUNG VON STICKOXYD IN SAUERSTOFF UND FENTANYL AUF DIE NIERENFUNKTION BEI KÜNSTLICH BELÜFTETEN HUNDEN

ZUSAMMENFASSUNG

Die wirkung einer grossen Dosis Fentanyl (25 μg kg^{-1}) wurden bei 10 Labradorhunden untersucht. Die Tiere wurden mit Stickoxyd in Sauerstoff und einer kleinen Zugabe von Fentanyl 0,4 μg min^{-1} während des ganzen Experiments narkotisiert, und Muskelentspannung wurde durch Alcuronium bewirkt; die Beluftung war kontrolliert. In der Anfangsphase eine jeden Experimentes wurden Nierenplasmastrom, Glomularfiltrierrate, Harnvolumen, mittlerer arterieller Druck und Nierengefässwiderstand in Abständen von 30 min gemessen, wobei 3 Satze von Proben entnommen wurden. Dann wurde die grosse Dosis Fentanyl über 10-min verabreicht, worauf die Messungen in Abständen von 30-min für einen Zeitraum von 90 min wiederholt wurden. Änderungen der Nierenfunktion dauerten etwa 90 min; es gab einen wesentlichen Abstieg des geschätzten Nierenplasmastromes ($P < 0{,}01$), Glomerularfiltrierrate ($P < 0{,}001$), Harnvolumen ($P < 0{,}01$) und mittleren arteriellen Druck ($P < 0{,}001$), zusammen mit einem Anstieg des Nierengefässwiderstandes ($0{,}05 > P > 0{,}02$). Begleitet wurden diese Veränderungen von Bradykardie, waren aber immer noch vorhanden, wenn Atropin verabreicht wurde.

EFECTO DE LA ANESTESIA CON OXIDO NITROSO EN OXIGENO Y FENTANILO SOBRE LA FUNCION RENAL EN EL PERRO ARTIFICIALMENTE VENTILADO

SUMARIO

Se averiguó en 10 perros Labrador el efecto sobre la función renal de una dosis mayor (25 μg kg^{-1}) de fentanilo. Los animales fueron anestesiados con óxido nitroso en oxígeno y un pequeño suplemento de fentanilo (0,4 μg min^{-1}) durante toda la duración del experimento, y se facilitó la relajación muscular por medio de alcuronio, controlándose la ventilación pulmonar. En la fase inicial de cada experimento, se midieron el flujo renal estimado, el ritmo de filtración glomerular, el volumen de orina, la presión arterial media y la resistencia vascular renal a intervalos de

30 min, y se tomaron tres series de muestras. Entonces, se administró una dosis fuerte de fentanilo a lo largo de un periodo de 10 min y se repitieron las mediciones a intervalos de 30 min durante 90 min. Los cambios en la función renal duraron alrededor de 90 min; hubo una disminución significativa del flujo plasmático renal estimado ($P < 0,01$), del ritmo de filtración glomerular ($P < 0,001$), del volumen de orina ($P < 0,01$) y de la presión arterial media ($P < 0,001$), junto con un aumento de la resistencia vascular renal ($0,05 > P > 0,02$). Estos cambios se acompañaron de una bradicardia, pero estaban aún presentes cuando se administró atropina.

Br. J. Anaesth. (1980), **52**, 349

PRELIMINARY *IN VITRO* STUDY OF DIAZEPAM AND DROPERIDOL ON OESTRUS RAT UTERUS

A. A. KHAN

SUMMARY

The actions of diazepam and droperidol were studied on the spontaneously active and oxytocin-treated oestrus rat uterus. Both drugs significantly depressed the frequency of uterine contraction. Droperidol reduced the amplitude of contractions and the basal tone of the tissue. The sensitivity of the tissue to both drugs was enhanced in the presence of the smallest concentration of oxytocin (0.2 mu. ml^{-1}). Prior exposure of the tissue to droperidol sensitized the muscle to oxytocin.

The increasing use of recently introduced compounds in obstetric practice, both by anaesthetists and by gynaecologists, has inevitably posed the question of the effect these may have on uterine contractility. Diazepam is used clinically in obstetrics and gynaecology as a sedative and as an anaesthetic induction agent. The butyrophenone, droperidol, is finding increasing favour as a premedicant and anti-emetic. Both these drugs, although chemically dissimilar, have been shown to have significant effects upon smooth muscle (Puddy, 1971; Greene, 1972; Bradshaw, 1978). In this preliminary study the effects of diazepam and droperidol have been examined on the spontaneously active or oxytocin-stimulated, isolated, oestrus rat uterus.

METHOD

The rat uterus was used in the oestrus condition as this is the stage when the uterus contracts most actively. The stage of the oestrus cycle was determined by the cornification index of the rat's vaginal smear. The rat was killed and each horn of the uterus was divided longitudinally to provide four preparations. These were suspended in Krebs–Henseleit solution, kept at 37 °C and bubbled with 5% carbon dioxide in oxygen. Each muscle strip was attached to a strain-gauge transducer connected to a Rikadenki pen recorder. One gram pre-load was used and measurements were taken of frequency and amplitude of contractions over a 15-min period, first in the control state, then with the drugs under study. Results are expressed as percentage change from pre-drug control. Since the activity of the spontaneously contracting preparation was short lived, each muscle strip was used for one concentration of drug or its solvent. Drug and solvent were tested on paired preparations.

The effects of the drugs were examined in preparations treated with two concentrations of oxytocin, 0.2 and 2 mu. ml^{-1}. Generally, oxytocin was added to the preparation after a response to the drug had been obtained in the spontaneously active uterus. Once treated with oxytocin the same preparation could be used for several concentrations of drug.

The number of experiments in each category varied between six and 20. The results were expressed as mean values ± SEM and significance was assessed using the Student's t test.

Drugs

Diazepam was used as the commercially available solution for parenteral injection and dilutions were made with distilled water.

Diazepam solvent—propylene glycol 41.4%, ethanol 8.1%, benzoic acid 0.12%, sodium benzoate 4.88%, benzyl alcohol 1.57% and water to 100%—was used in volumes equivalent to that present in the diazepam concentrations used in the study.

Droperidol was used as the commercially available solution for parenteral injection and diluted with distilled water.

Droperidol solvent, which contains lactic acid, methyl-p-hydroxybenzoate and propyl-p-hydroxybenzoate, was supplied by Janssen Ltd and used in concentrations equivalent to those present in droperidol.

ALAM A. KHAN, F.R.C.S.(ED.), F.F.A.R.C.S., M.R.C.O.G.; Departments of Anaesthetics and Pharmacology, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT.

0007–0912/80/030349–06 $01.00

© Macmllian Journals Ltd 1980

RESULTS

Diazepam

There was an overall depression of frequency of myogenic activity with diazepam which was significant even with 1 μg ml^{-1} ($P < 0.05$) (fig. 1). The activity of the uterus was minimal with diazepam 64 μg ml^{-1}. The preparation bathed in the smaller concentration of oxytocin, 0.2 mu. ml^{-1}, was more effectively depressed by diazepam than either the spontaneously active muscle strip or that stimulated with the greater concentration of oxytocin ($P < 0.05$ for the 8- and 16-μg ml^{-1} concentrations of diazepam).

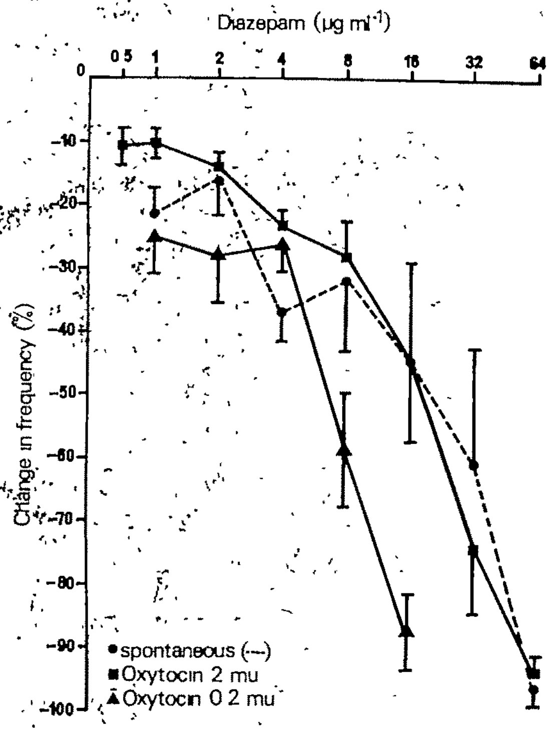


FIG. 1. Diazepam on the frequency of the myogenic activity of the spontaneously active and oxytocin-stimulated oestrus rat uterus. Results are mean values ± SEM of not less than eight experiments. All points illustrate statistically significant reductions in frequency of contractions (*P* varies in the range < 0.05–< 0.001).

There was no significant difference between the pre-drug frequency of contractions in spontaneously active preparations (mean 14.5 ± 0.48, $n = 100$) and preparations treated with oxytocin 0.2 mu. ml^{-1} (mean 15.8 ± 0.8, $n = 19$).

Diazepam did not show a significant effect upon the mean amplitude of the uterine contraction, either alone or in the presence of oxytocin (table I).

The effect of diazepam solvent was similar to that of the drug itself, but the degree of depression of frequency was smaller than with diazepam (table II). Like diazepam, it did not affect the mean amplitude of contraction significantly (table I).

Droperidol

It soon became evident that the solvent for droperidol did not have any influence on the rat uterine muscle activity. The study of this agent was, therefore, abandoned half way through the series.

The effect of droperidol on the frequency of contractions varied with concentration (fig. 2).

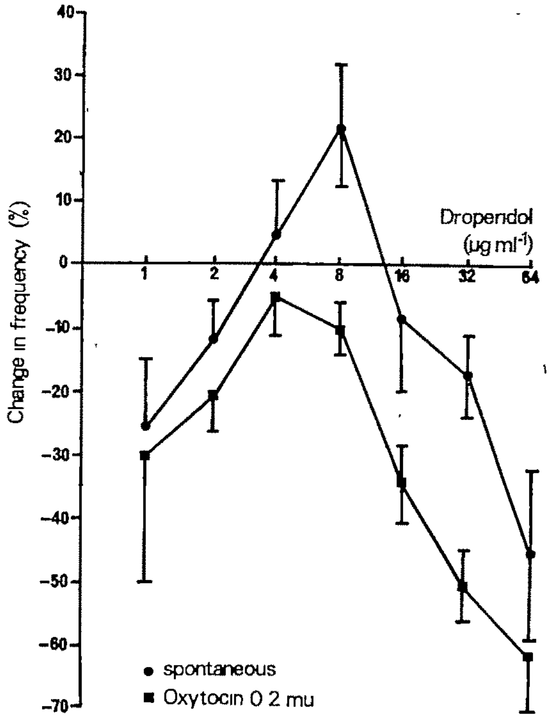


FIG. 2. Droperidol on the frequency of the myogenic activity of the spontaneously active and oxytocin 0.2 mu. ml^{-1}-stimulated oestrus rat uterus. Results are mean values ± SEM of not less than eight experiments.

Small and very great concentrations of droperidol appeared to depress the frequency, whilst equivocal effects were seen with 4 and 16 μg ml^{-1}. Droperidol 8 μg ml^{-1} appeared to increase the contraction rate ($P < 0.1 > 0.05$). When stimulated with the smaller concentration of oxytocin, 0.2 mu. ml^{-1}, the response of the uterus to droperidol was unchanged between 1 and 4 μg ml^{-1}. Droperidol 8–32 μg ml^{-1} depressed

TABLE I. *Diazepam and its solvent on the amplitude (g) of the myogenic activity of the spontaneously active and oxytocin-treated oestrus rat uterus*

	Change in amplitude (%) (mean ± SEM)					
	Spontaneous	*n*	Oxytocin 0.2 mu. ml^{-1}	*n*	Oxytocin 2 mu. ml^{-1}	*n*
Diazepam (μg ml^{-1})						
1	−25.0 ± 14.4	6	− 3.5 ± 2.7	6	− 1.0 ± 5.2	11
2	−13.4 ± 12.4	6	− 6.1 ± 2.3	9	− 3.1 ± 5.2	10
4	−11.0 ± 13.3	6	− 2.7 ± 2.2	7	− 5.9 ± 2.6	10
8	−19.5 ± 11.1	6	− 1.6 ± 1.1	12	−12.0 ± 4.8	6
16	−16.8 ± 7.7	6	−11.6 ± 8.2	8	−23.8 ± 8.1	6
32	−15.7 ± 15.6	13	no activity	20	−14.8 ± 5.2	8
64	no activity	6	no activity	20	−14.2 ± 1.0	11
Solvent (volume equivalent to diazepam μg ml^{-1})						
1	+ 4.8 ± 3.7	6	+5.3 ± 1.9	6	−3.2 ± 3.8	11
2	+ 1.6 ± 9.6	6	+5.1 ± 3.5	9	+2.3 ± 1.5	10
4	− 4.7 ± 4.5	6	−2.9 ± 3.1	7	+4.7 ± 2.5	10
8	+ 9.4 ± 7.2	6	−2.0 ± 3.5	12	+7.2 ± 2.2	6
16	− 5.8 ± 4.5	6	−1.1 ± 2.5	8	−2.4 ± 2.3	6
32	− 4.3 ± 2.5	13	—	20	−2.9 ± 2.8	8
64	−18.7 ± 8.2	6	—	20	+0.6 ± 3.2	11

TABLE II. *Diazepam solvent on the frequency of the myogenic activity of the spontaneously active and oxytocin-treated oestrus rat uterus*

	Change in frequency (%) (mean ± SEM)					
	Spontaneous	*n*	Oxytocin 0.2 mu. ml^{-1}	*n*	Oxytocin 2 mu. ml^{-1}	*n*
Solvent (volumes equivalent to diazepam μg ml^{-1})						
1	− 3.6 ± 7.7	6	−23.6 ± 6.5	6	− 6.4 ± 2.5	11
2	−24.3 ± 5.5	6	−23.0 ± 7.6	9	− 8.3 ± 1.1	10
4	−13.9 ± 7.1	6	−21.0 ± 4.1	6	−12.0 ± 1.3	10
8	−36.7 ± 6.5	6	−36.0 ± 4.0	14	−14.9 ± 2.3	6
16	+ 3.1 ± 3.8	6	−28.8 ± 10.2	8	−18.3 ± 2.5	6
32	− 4.7 ± 5.2	8	—	20	−30.7 ± 8.0	8
64	−33.5 ± 17.9	6	—	20	−27.4 ± 4.7	11

TABLE III. *Droperidol on the amplitude of myogenic activity in the spontaneously active and oxytocin-treated oestrus rat uterus*

	Change in amplitude (%) (mean ± SEM)					
	Spontaneous	*n*	Oxytocin 0.2 mu. ml^{-1}	*n*	Oxytocin 2 mu. ml^{-1}	*n*
Droperidol (μg ml^{-1})						
1	+ 0.2 ± 5.2	6	− 8.7 ± 24.2	6	+ 5.9 ± 4.7	8
2	+ 5.1 ± 3.1	8	−15.9 ± 10.5	11	+16.9 ± 6.6	8
4	+ 4.2 ± 6.5	8	−13.1 ± 6.7	12	+70.1 ± 66.6	8
8	− 2.2 ± 4.6	6	− 3.1 ± 5.1	12	− 0.4 ± 6.1	6
16	−22.5 ± 7.0	6	−21.7 ± 4.9	12	+ 1.8 ± 26.1	7
32	−32.5 ± 9.0	6	−40.8 ± 5 6	12	−19.5 ± 19.9	9
64	−43.5 ± 8.4	6	−46.6 ± 7.8	12	no activity	6

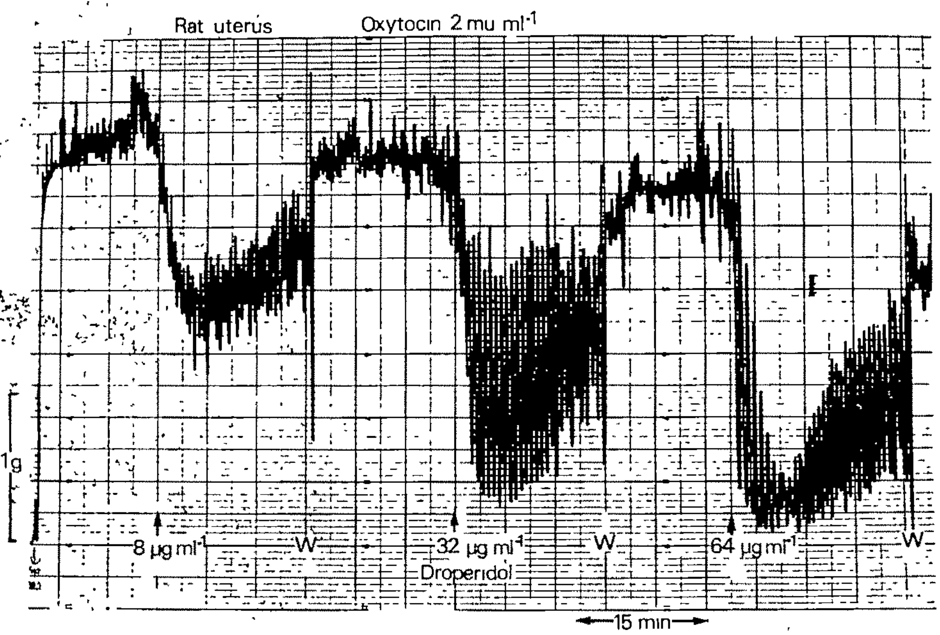


FIG. 3. Example of trace showing the effect of droperidol on the rat uterus, previously exposed to droperidol, washed and then treated with oxytocin 2 mu. ml⁻¹.

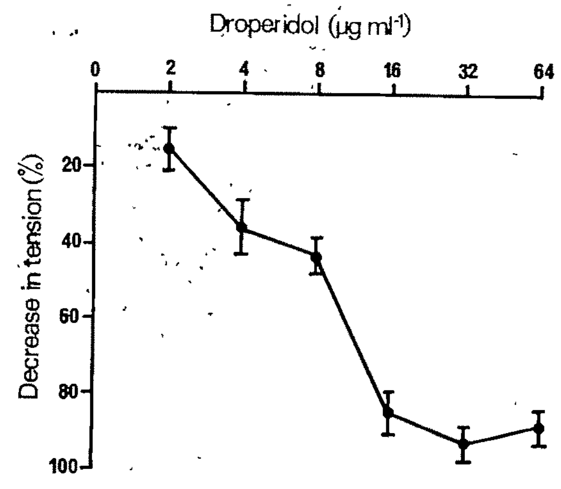


FIG. 4. Droperidol on the increase in baseline tension produced by oxytocin 2 mu. ml⁻¹ on the droperidol-primed (see text) oestrus rat uterus. Results are mean values ± SEM of not less than six experiments.

the oxytocin-stimulated preparation more than the spontaneously active uterus ($P < 0.05$).

In contrast to diazepam, droperidol caused significant decreases in the mean amplitude of the spontaneous and oxytocin 0.2 mu. ml⁻¹-treated uterus (table III). This only occurred with large concentrations of the drug.

If the preparation had previously been treated with droperidol, despite intensive washing, oxytocin 2 mu. ml⁻¹ sent the muscle into tetanic spasm in most preparations. Paired preparations, pretreated with droperidol solvent, did not exhibit this tetanic response to oxytocin. In the tetanic preparation a quantitative assessment of the effects of droperidol on the frequency of contractions was not possible (fig. 3). Some attempt was made to quantify the effect on amplitude, but as can be seen from table III, no clear conclusions could be drawn. However, droperidol did cause a concentration-dependent reversal of the increase in baseline tension produced by oxytocin 2 mu. ml⁻¹ (fig. 4).

DISCUSSION

Only the frequency of uterine contraction was depressed by diazepam in this study. Thus, it may be that diazepam interferes with the pacemaker for myogenic activity rather than the ability of the muscle cells to contract. Toaff, Hezroni and Toaff (1977) have demonstrated that 10 mg of diazepam i.v. inhibited the frequency of uterine contraction during human labour.

Uterine muscle treated with a small concentration of oxytocin was more sensitive to the depressant effects of diazepam. This observation may support the impression of Landesman and Wilson (1965) that diazepam 5 $\mu g\ ml^{-1}$ blocked contractions in 58% of specimens of uterine muscle from pregnant women, compared with 12% of the non-gravid sample. Furthermore, the clinical work of Berger, quoted by Caldeyro-Barcia (1965), suggests an effect of diazepam on the hypertonic uterus which is compatible with the present study. Berger found no effect of diazepam on the basal tone of pregnant human uterus when this was normal, but in 30 cases of pathological hypertonus, he succeeded in decreasing it to normal with an i.v. injection of 30 mg of diazepam. The hypertonia reflects the sensitivity of the uterus to oxytocic stimuli.

The relevance of the concentrations of drugs used in the present study to clinical practice is difficult to assess. The quantity of drug necessary to produce a clinical response in the rat is usually much greater, on a weight-to-weight basis, than it is in man. Second, it is difficult to know the proportion of a drug reaching the uterus after systemic administration. Nevertheless, the concentrations of diazepam used in this study are similar to those used by other workers (Todd and Cavanagh, 1964; Landesman and Wilson, 1965; Achim et al., 1969).

Consistent effects with droperidol were seen only with greater concentrations in this study. The interesting feature was that, in contrast to diazepam, all aspects of muscle activity (frequency, amplitude and basal tone) were depressed. Similar findings have been reported in human subjects (Romero-Salinas et al., 1973).

The sensitivity of the rat uterus to droperidol was increased in the presence of oxytocin 0.2 mu. ml^{-1}. The tetanic response of the droperidol-primed tissue to the greater concentration of oxytocin was surprising, especially when the subsequent relaxant effect of droperidol on the muscle was considered. Further work is necessary to clarify the mechanism of these effects, particularly to determine whether prostaglandin activity is involved.

ACKNOWLEDGEMENTS

I wish to acknowledge the very considerable help and encouragement given me by Dr Barbara Pleuvry of the Departments of Pharmacology and Anaesthetics, University of Manchester, and the assistance of her staff, particularly Miss Stephanie Maddison.

REFERENCES

Achim, V., Ardeleanu, C., Petrescu, V., and Manolescu, E. (1969). Cercetări experimentale şi clinice privind acţiunea diazepamului (Valium) asupra contracţiei uterine. *Obstet. Ginec.*, **17**, 553.

Bradshaw, E. G. (1978). Studies of the pharmacology of diazepam in animals and man relevant to anaesthetic practice. M.D. Thesis, University of London.

Caldeyro-Barcia, R. (1965). Résumé critique; in La physiopathologie de la contraction utérine. III: Action du Valium en Obstetrique. *Bull. Fed. Gyn. Obst. Franç.*, **17**, 451.

Greene, M. J. (1972). Some aspects of the pharmacology of droperidol. *Br. J. Anaesth.*, **44**, 1272.

Landesman, R., and Wilson, K. H. (1965). Relaxant effects of diazepam on uterine muscle. *Obstet. Gynecol.*, **26**, 552.

Puddy, B. R. (1971). Effects of droperidol on the vasoconstriction produced by noradrenaline, histamine, sympathetic nerve stimulation and potassium ion in the isolated rabbit auricular artery. *Br. J. Anaesth.*, **43**, 441.

Romero-Salinas, G., Perez-Tamayo, L., Ruiz-Velasco, V., Moreno-Martinez, O., Bravo-Sandoval, J., and Cruz-Montes, G. (1973). El dehydrobenzperidol y su effecto sobre la contractilidad del utero humano no gravida. *Ginec. Obstet. Mex.*, **34**, 389.

Toaff, M. E., Hezroni, J., and Toaff, R. (1977). Effect of diazepam on uterine activity during labour. *Israel J. Med. Sci.*, **13**, 1007.

Todd, J. M., and Cavanagh, D. (1964). The effects of diazepam and chlordiazepoxide on isolated human myometrium. *Bull. Univ. Miami Sch. Med.*, **18**, 25.

ETUDE PRELIMINAIRE *IN VITRO* DU DIAZEPAM ET DU DROPERIDOL SUR L'UTERUS DU RAT ŒSTRE

RESUME

On a procédé à des études de l'action du diazépam et du dropéridol sur l'utérus d'un rat œstre traité à l'oxytocine et spontanément actif. Les deux substances eurent pour effet une dépression significative de la fréquence des contractions utérines. Le dropéridol diminua l'amplitude des contractions et le ton basal du tissu. La sensitivité du tissu aux deux substances fut rehaussée en présence de la moindre concentration d'oxytocine (0,2 mu. ml^{-1}). Une exposition préalable du tissu au dropéridol a sensibilisé le muscle à l'oxytocine.

PRÄLIMINARSTUDIE *IN VITRO* DER WIRKUNGEN VON DIAZEPAM UND DROPERIDOL AUF DEN UTERUS VON OESTRUS-RATTEN

ZUSAMMENFASSUNG

Die Wirkungen von Diazepam und Droperidol auf den spontan aktiven und mit Oxytocin behandelten Uterus der Oestrus-Ratte wurden untersucht. Beide Drogen unterdrückten deutlich die Häufigkeit uteriner Kontraktionen. Droperidol verringerte die Kontraktionsamplitude und den basalen Gewebetonus. Die Gewebeempfindlichkeit auf beide Drogen wurde durch die Anwesenheit der geringsten

Konzentration von Oxytocin (0,2 mu. ml^{-1}) erhöht. Vorherige Einwirkung von Droperidol auf das Gewebe erhöhte die Empfindlichkeit des Muskels auf Oxytocin.

ESTUDIO PRELIMINAR *IN VITRO* DEL DIAZEPAM Y DEL DROPERIDOL SOBRE EL UTERO DE UN RATON ESTRO

SUMARIO

Se llevó a cabo el estudio de las acciones del diazepam y del droperidol sobre el útero de un ratón estro tratado con oxitocina y espontáneamente activo. Ambas substancias deprimieron significativamente la frecuencia de las contracciones uterinas. El droperidol redujo la amplitud de las contracciones y el tono basal del tejido. La sensibilidad del tejido para con ambas substancias fue realizada en presencia de la más baja concentración de oxitocina (0,2 mu. ml^{-1}). Una exposición previa del tejido al droperidol sensibilizó el músculo a la oxitocina.

Br. J. Anaesth. (1980), **52**, 355

CORRESPONDENCE

ANAPHYLACTOID TYPE ADVERSE RESPONSES

Sir,—The letter of Watkins, Thornton and Clarke (1979) states correctly that the mechanism of anaphylactoid type adverse responses to anaesthetic agents is not necessarily a result of IgE-mediated anaphylaxis. They therefore feel that the "claims made for skin testing must be viewed with a great deal of scepticism".

The goals in investigating a patient after such a reaction are to determine the nature of the reaction and, more importantly when more than one drug is used, to determine the drug responsible.

For 6 years we have used intradermal testing following a strict protocol in an effort to fulfil both goals. The results, methods and details of confirmation have been published in detail (Fisher, 1978, 1979) and the results to date are summarized in table I.

This table supports the conclusion that intradermal testing is a reliable way of determining the cause of reactions to myoneural blocking drugs, although less valuable with induction agents, and appears to be of no value after reactions to colloids, contrast media and local analgesic drugs. This is particularly relevant in Australasia, where the majority of reactions in the past 2 years have been caused by neuromuscular blocking drugs.

TABLE I. *Results of intradermal testing in* 78 *consecutive patients*

* *Four results flare only absent from controls*;

** *confirmed by administering same agents on a subsequent occasion*

	No. tested	Positive	Confirmed
Thiopentone	3	3	2
Propanidid	2	0	—
Althesin	14	10*	10
Alcuronium	9	9	8
Pancuronium	1	1	1
Suxamethonium	7	7	6
Tubocurarine	4	4	3
Gallamine	7	7	6
Local anaesthesia	3	0	—
Contrast media	3	1	1
Colloid solution	4	0	—
No result:			
Multiple drugs	5		
Probable genuine reaction			
No result:			
Probable alternative cause	16	0	15**

Intradermal testing will not always provide an answer, but its low cost, ease of performance and interpretation, and safety permit a useful practical manoeuvre, particularly if laboratory services are not available.

These results are not confined to our own practice, and the usefulness of such testing has been well documented by others (Brown, 1975; Mandappa, Chandrasekhara, and Nelvigi, 1975; Evans and McKinnon, 1977; Mathews, Ceglarski and Pabari, 1977; Brauer and Ananthanarayan, 1978; McKie, 1978; Royston and Wilkes, 1978; James et al., 1979; Long, 1979).

The charge of prejudgement of mechanisms is only partly true. Historically, we began intradermal testing in 1972 in an effort to find a way of determining the drug responsible in what was an almost completely unknown area, and were indeed fortunate that the reactions in the first patients tested were probably IgE-mediated. The continuing experience illustrated in the table, and the reports and personal communications of others, have encouraged us to persist. There is circumstantial evidence that the majority of reactions to relaxants and a proportion of those to induction agents are true IgE-mediated reactions (Fisher, 1978, 1979, in preparation) and we believe intradermal testing to be justified on this basis alone.

M. Fisher
St Leonard's, Australia

REFERENCES

Brauer, F. S., and Ananthanarayan, C. R. (1978). Histamine release by pancuronium. *Anesthesiology*, **49**, 434.

Brown, T. P. (1975). Thiopentone anaphylaxis. *Anaesth. Intens. Care*, **3**, 257.

Evans, P. D. J., and McKinnon, I. (1977). An anaphylactoid reaction to gallamine triethiodide. *Anaesth. Intens. Care*, **5**, 239.

Fisher, M. McD. (1978). Intradermal testing in the diagnosis of allergic reactions to intravenous drugs; in *Adverse Reactions to Intravenous Drugs* (eds J. Watkins and A. Milford Ward), p. 137. London: Academic Press.

—— (1979). Intradermal testing in the diagnosis of acute anaphylaxis during anaesthesia. Results of five years experience. *Anaesth. Intens. Care*, **7**, 58.

James, O. F., Aservathain, B., Fortunaso, B., and Clancy, R. (1979). Anaphylactoid reaction to suxamethonium. *Anaesth. Intens. Care*, **7**, 288.

Long, G. T. (1979). Reactions to gallamine. *Anaesth. Intens. Care*, **7**, 191.

McKie, D. D. (1978). Anaphylactic reactions to gallamine. *Anaesth. Intens. Care*, **6**, 266.

Mandappa, J. M., Chandrasekhara, P. M., and Nelvigi, R. G. (1975). Anaphylaxis to suxamethonium: two case reports. *Br. J. Anaesth.*, **47**, 523.

Mathews, M., Ceglarski, M., and Pabari, M. (1977). Anaphylaxis to suxamethonium—a case report. *Anaesth. Intens. Care*, **5**, 235.

Royston, D., and Wilkes, R. G. (1978). True anaphylaxis to suxamethonium chloride. *Br. J. Anaesth.*, **50**, 611.

Watkins, J., Thornton, J. A., and Clarke, R. S. J. (1979). Adverse reactions to i.v. agents. *Br. J. Anaesth.*, **51**, 469.

EQUATIONS

Sir,—Rodgers and Hill (1978) offered a collection of clinically useful equations in their recent article. I believe that three of these equations are in error. Equation (8) incorrectly relates the flow of gas into the vaporizer (F_V), the final anaesthetic concentration in per cent (M), the vapour pressure of the anaesthetic (p_V), the atmospheric pressure (p_A) and the total gas flow (F_T):

$$F_V = \left(\frac{p_A}{p_V}\right) F_T \left(\frac{M}{100}\right) \qquad \text{Rodgers and Hill's equation (8) (incorrect)}$$

This error is propagated to their next equation when they conclude:

$$F_R = F_T\left[1 - \frac{M}{100}\left(\frac{p_A + p_V}{p_V}\right)\right] \qquad \text{Rodgers and Hill's equation (9) (incorrect)}$$

where F_R is the remainder flow in the system.

I offer the following derivation for the correction of the above equations.

The anaesthetic–vapour fraction of the total gas leaving the vaporizer is given by p_V/p_A (fraction by pressure) and by $F_A/(F_A + F_V)$ (fraction by flow). Equating these two fractions and solving for F_A gives:

$$F_A = F_V\left(\frac{p_V}{p_A - p_V}\right) \qquad \text{equation 1}$$

and as correctly noted by Rodgers and Hill:

$$M = \left(\frac{F_A}{F_T}\right) 100 \Rightarrow$$

$$F_A = \left(\frac{M}{100}\right) F_T \qquad \text{equation 2}$$

Substituting equation 2 for F_A in equation 1 and solving for F_V gives:

$$F_V = \left(\frac{p_A - p_V}{p_V}\right) F_T \left(\frac{M}{100}\right) \qquad \text{equation 3 (Rodgers and Hill's equation (8) corrected)}$$

Since the total flow must equal the sum of its parts:

$$F_T = F_R + F_A + F_V \qquad \text{equation 4}$$

I can conclude:

$$F_R = F_T\left[1 - \frac{M}{100}\left(\frac{p_A}{p_V}\right)\right] \qquad \text{equation 5 (Rodgers and Hill's equation (9) corrected)}$$

Equation 5 is an important correction for both theoretical and practical reasons. For example: at 22 °C, 760 mm Hg, 5000 ml remainder flow and 100 ml vaporizer flow, Rodgers and Hill's equation (9) predicts a halothane concentration of 0.77% when the actual concentration is 1.04%— an error of 26%.

The third erroneous equation in Rodgers and Hill's article incorrectly gives the maximal attainable percentage concentration (equation (7)). By simply substituting in equation 5 above a zero background flow ($F_R = 0$), one can easily demonstrate

$$M_{\max} = \left(\frac{p_V}{p_A}\right) 100 \qquad \text{equation 6 (Rodgers and Hill's equation (7) corrected)}$$

because when $F_R = 0$, F_T must equal $F_V + F_A$.

Since F_T is not known exactly during the course of the usual clinical anaesthetic, I suggest putting equation 5 in a more useful form by relating parameters which are known or determined arbitrarily (F_R, M, F_V, p_A, p_V).

Substituting equation 1 in 4 and then 4 in 3 gives:

$$F_V = \left(\frac{p_A - p_V}{p_V}\right)\left[F_R + F_V + F_V\left(\frac{p_V}{p_A - p_V}\right)\right]\frac{M}{100} \Rightarrow$$

$$F_R = F_V\left(\frac{p_V}{p_A - p_V}\right)\left(\frac{100}{M} - \frac{p_A}{p_V}\right) \qquad \text{equation 7}$$

In this form, equation 7 can be readily used in the operating room. With a hand-held programmable calculator, one can combine equation 7 and the Antoine equation as given by Rodgers and Hill to calculate the effect of temperature, altitude, anaesthetic vapour pressure and gas flows on the concentration of anaesthetic vapour delivered to the patient.

Michael K. Cahalan
San Francisco, U.S.A.

REFERENCE

Rodgers, R. C., and Hill, G. E. (1978). Equations for vapour pressure versus temperature: derivation and use of the Antoine equation on a hand-held programmable calculator. *Br. J. Anaesth.*, **50**, 415.

Sir,—Dr Cahalan has correctly pointed out errors in our formulae (7)–(9). His example of the difference in results for halothane is slightly misleading, as for any set values of total flow and flow to the vaporizer, the value of percent anaesthetic calculated by our formulation (M_R) will differ from his estimate (M_C) as follows:

$$\frac{p_A}{p_A - p_V} M_R = M_C \qquad (1)$$

That is to say, the relative error is *independent* of the flows in the system, and depends upon the magnitude of the vapour pressure of the anaesthetic agent. Were methoxyflurane used in his example rather than halothane, the error in estimating M would be only roughly 3%.

We thank Dr Cahalan for his corrections, and hope that they will not detract from the main achievement of our study: to consolidate literature on vapour pressure data, and to make the Antoine equation a readily accessible clinical tool rather than a researcher's curiosity.

R. P. Channing Rodgers
Bethesda, U.S.A.

ENFLURATEC VAPORIZER

Sir,—Halothane is known to leak in trace amounts from Fluotec 3 vaporizers in good condition (Robinson, Thompson and Barratt, 1977) and inaccuracy as a result of misuse has been reported (Marks and Bullard, 1976). I wish to report a fault in a very similar vaporizer, the Enfluratec, which caused it to deliver an unknown, but clinically significant, concentration of enflurane, when apparently turned off.

The construction of the Enfluratec is very similar to that of the Fluotec Mk 3 described by Paterson, Hulands and Nunn (1969). It differs in the calibration of the concentration setting dial and in having a steel spring, working on a plastic cam under the dial, which limits rotation of the dial and allows it to be locked OFF. The cam is fixed to the dial by two screws, but in the faulty vaporizer one had fallen out, into the top of the casing. With the cam loose, it was possible to turn the dial a few degrees clockwise beyond the OFF position, when a strong smell of enflurane was noticed in the fresh gas flow. Anaesthetists should be aware that unless the OFF mark on the concentration setting dial coincides with the datum mark, then their Enfluratec or, presumably, Fluotec 3, may still deliver vapour.

I have reported this finding to Cyprane, making two suggestions. First, all existing Enfluratecs should be modified by fixing the cam to the dial by *four* instead of two screws. The cam and dial are already drilled and tapped for this, the extra holes being used at present to attach the name-plate to the dial.

Second, the present design, with a hard steel spring working on a soft plastic cam, seems unsatisfactory and bound to cause excessive wear. The cam on the faulty vaporizer was badly worn after only 8 months' use. The rim of the concentration setting dial could be used as a cam, with different machining for different models, from the same stock of parts. A spring made of plastic in the same way as the one-piece hinges found on some plastic boxes would avoid the wear problem.

J. R. Davies
Stockholm, Sweden

REFERENCES

Marks, W. E., and Bullard, J. R. (1976). Another hazard of free-standing vaporizers: increasing anesthetic concentration with reversed flow of vaporizing gas. *Anesthesiology*, **45**, 445.

Paterson, G. M., Hulands, G. H., and Nunn, J. F. (1969). Evaluation of a new halothane vaporizer: the Cyprane Fluotec Mark 3. *Br. J. Anaesth.*, **41**, 109.

Robinson, J. S., Thompson, J. M., and Barratts, R. S. (1977). Inadvertent contamination of anaesthetic circuits with halothane. *Br. J. Anaesth.*, **49**, 745.

Sir,—Unfortunately we have not had the opportunity to examine the Enfluratec with which Dr Davies experienced his reported problems, but we have tried removing the stop mechanism completely from another Enfluratec to examine the performance under these conditions. With steady-state conditions we were unable to detect any measurable concentration of Enflurane below the OFF position until the dial had been turned approximately 90° below OFF where a concentration of approximately 1% was observed. As the dial was rotated further the concentration again decreased to zero until the maximum graduation of the scale was approached from the reverse direction when the concentration suddenly increased to 7%. The apparatus used for these measurements was sensitive to concentrations of approximately 0.01% enflurane.

In a correctly functioning Enfluratec, the port which permits the flow of fresh gases into the vaporizing chamber is closed by the rotary valve from the position 90° below OFF to a position close to the lowest graduated mark on the scale. Our belief is that Dr Davies may have been observing either trace concentrations of the type reported by Robinson, Thompson and Barratt (1977), or minor surges which could occur if the inlet connected to the vaporizing chamber is closed off, but the outlet port is open. Such surges would be of short duration. The precise time depends on a number of factors such as the circuit configurations and pressure in the circuit.

Any minor misalignment of a few millimetres of the OFF mark and the scale pointer, will not in itself result in the delivery of clinically significant concentrations as in this case both the inlet port to and the outlet port from the vaporizing chamber are closed by the rotary valve. If for any reason the dial can be turned approximately 5 mm below the OFF mark, it is conceivable that intermittent pressure surges or diffusion could result in the delivery of very small concentration of enflurane indicated by a smell of enflurane at the outlet. A through flow fo fresh gases through the vaporizing chamber could not occur because the inlet to the vaporizing chamber is closed by the rotary valve.

Dr Davies makes a number of positive suggestions for design modification and it is interesting to note that since the date of manufacture of this particular vaporizer we have made a number of modifications, namely:

(1) Using a much tougher material for the stop/control ring.
(2) Fitting flanges on the leaf spring.

These modifications were introduced as a result of our observations of very occasional heavy wear which only became evident after examining many thousands of Fluotec Mk 3 vaporizers passing through our Cyprane Service Centres (covering more than 20 countries). Modifications of the type indicated above are automatically incorporated into vaporizers at the time of annual servicing at Cyprane Service Centres and this fact alone demonstrates to both manufacturers and users of equipment the value of regular preventative maintenance.

It is very difficult to comment on how the particular screw in question could become loose without a detailed examination of the vaporizer. However, we can confirm that Cyprane, and its overseas Service Centres, have been unable to identify any general problem of security of this item.

We have, however, taken note of Dr Davies' comments and have introduced a minor modification to the security of attachment of the stop control ring.

We would like to emphasize that, in common with most manufacturers, we occasionally carry out minor design changes even to products which may be very reliable. Where these are of functional importance it is our normal practice to incorporate these changes into vaporizers returned to our Service Centres wherever practicable at the time of annual service.

R. W. Carter
Cyprane Ltd, Keighley, Yorks

REFERENCE

Robinson, J. S., Thompson, J. M., and Baratt, R. S. (1977). Inadvertent contamination of anaesthetic circuits with halothane. *Br. J. Anaesth.*, **49**, 745.

ANALGESIC ACTION OF EXTRADURAL FENTANYL

Sir,—Animal studies have shown that morphine acts selectively on the nociceptive receptors in the dorsal horns of the spinal column (Yaksh and Rudy, 1976a; Yaksh, 1978; Yaksh and Henry, 1978). Following these reports there has been increasing interest in the clinical application of intrathecal narcotics (Yaksh and Rudy, 1976b; Behar et al., 1979; Samii et al., 1979; Wang, Nauss and Thomas, 1979).

In a previous communication by Wolfe and Nicholas (1979), it was reported that satisfactory analgesia was

TABLE I. *Plasma fentanyl concentrations (μg litre^{-1}) in eight patients following the administration of fentanyl 0.1 mg diluted with 0.9% sodium chloride 8 ml into the extradural space. The sensitivity of the assay method was 0.15 μg litre^{-1}*

Surgical procedure	Time from extradural injection (min)					
	5	10	20	30	60	120
Caesarean section	0.76	0.17	0.18	0.16	<0.15	<0.15
Caesarean section	<0.15	<0.15	<0.15	<0.15	<0.15	<0.15
Caesarean section	<0.15	<0.15	<0.15	<0.15	<0.15	<0.15
Caesarean section	<0.15	<0.15	<0.15	<0.15	<0.15	<0.15
Lobectomy	0.42	<0.15	<0.15	<0.15	<0.15	<0.15
Pleurectomy	1.02	4.10	1.56	1.24	0.92	—
Lobectomy	0.84	0.96	0.72	0.22	1.86	1.08
Lobectomy	0.34	0.72	0.46	0.34	0.32	0.24

obtained in 20 consecutive patients undergoing Caesarean section, using extradural fentanyl as the major analgesic after operation. To date our study now totals 40 obstetric and 20 thoracic cases; all of the patients were extremely satisfied with the analgesia obtained and did not demonstrate any adverse cardiorespiratory effects such as those described by other workers using different opiates (Glynn et al., 1979; Liolios and Andersen, 1979; Scott and McClure, 1979.

Encouraged by these results, but uncertain as to the exact role, if any, of plasma absorption of fentanyl we measured plasma fentanyl concentrations in eight patients; in four, Caesarean section had been performed under extradural analgesia with bupivacaine and the remainder had undergone thoracotomy with general anaesthesia. None of the patients received an opiate before or during operation until the administration of fentanyl 0.1 mg diluted in 0.9% sodium chloride solution 8 ml which was given shortly after the cessation of surgery. Injection was through an extradural catheter inserted at L2–3 in the obstetric group and T6–7 in the thoracic group. Blood samples were taken at the time intervals shown in table I and the plasma fentanyl concentrations were measured using the method described by McQuay and others (1979). The minimum concentration detectable by the assay method was 0.15 μg litre^{-1}.

The results are from a small sample and statistical analysis is inappropriate. However, with the possible exception of the sixth patient, all results show virtually insignificant concentrations of plasma fentanyl, perhaps not surprising in view of its high lipid solubility compared with other opiates (Hollt and Teschemacher, 1975). Even the solitary value of 4.1 μg litre^{-1} in the sixth patient is probably less than that associated with an analgesic plasma concentration (R. F. Cookson, personal communication) and most unlikely to produce respiratory depression.

If fentanyl and other narcotics diffuse through the dura, as has been proposed, it would be interesting to know more about the limits of dosage compatible with the absence of undesirable side-effects, and also the extent to which volume of administered drug affects the spread of analgesic block as is the case with local anaesthetics injected to the extradural space.

M. J. WOLFE
G. K. DAVIES
Sheffield

REFERENCES

Behar, M., Olshwang, D., Magora, F., and Davidson, J. T. (1979). Epidural morphine in treatment of pain. *Lancet*, **1**, 527.
Glynn, C. J., Mather, L. E., Cousins, M. J., Wilson, P. R., and Graham, J. R. (1979). Spinal narcotics and respiratory depression. *Lancet*, **2**, 356.
Höllt, V., and Teschemacher, H. (1975). Hydrophobic interactions responsible for unspecific binding of morphine-like drugs. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **288**, 163.
Liolios, A., and Andersen, F. H. (1979). Selective spinal analgesia. *Lancet*, **2**, 357.
McQuay, H. J., Moore, R. A., Paterson, G. M. C., and Adams, A. P. (1979). Plasma fentanyl concentrations and clinical observations during and after operation. *Br. J. Anaesth.*, **51**, 543.
Samii, K., Feret, J., Harari, A., and Viars, P. (1979). Selective spinal analgesia. *Lancet*, **1**, 1142.
Scott, D. B., and McClure, J. (1979). Selective epidural analgesia. *Lancet*, **1**, 1410.
Wang, J. K., Nauss, L. A., and Thomas, J. E. (1979). Pain relief by intrathecally applied morphine in man. *Anesthesiology*, **50**, 149.
Wolfe, M. J., and Nicholas, A. D. G. (1979). Selective epidural analgesia. *Lancet*, **2**, 150.
Yaksh, T. L. (1978). Analgesic actions of intrathecal opiates in cat and primate. *Brain Res.*, **153**, 205.
—— Henry, J. L. (1978). Antinociceptive effects of intrathecally administered β-endorphin in the rat and cat. *Can. J. Physiol. Pharmacol.*, **56**, 754.
—— Rudy, T. A. (1976a). Intrathecal narcotics. *Pain*, **4**, 299.
—— —— (1976b). Analgesia mediated by a direct spinal action of narcotics. *Science*, **192**, 1352.

METALLIZED PLASTIC SHEETING

Sir,—I believe that the article by Radford and Thurlow (1979) concerning the use of metallized plastic sheeting in the prevention of hypothermia during surgery should be read in conjunction with that of a theatre electrocution (Chambers and Saha, 1979).

Several years ago my surgical colleagues suggested that space blankets might counteract peripheral vasoconstriction during vascular surgery. Having previous experience of a diathermy burn in a patient, which resulted in a fatality, I first wrote to the Technical Department of the D.H.S.S., and the essence of the reply I received was: "the insulation layer in metallized plastic films is so thin that breakdown is inevitable. Under no circumstances should such blankets be used in conjunction with surgical diathermy due to the serious risk of diathermy burns from aberrant earthing."

I apologize for my intellectual isolation in only banning space blankets from Lewisham District theatres. Obviously theatre users elsewhere need to be reminded of the electrical hazards of space blankets used with diathermy and metal operating tables. Indeed, if the practice is widespread, as your authors suggest, then a hazard warning notice from the D.H.S.S. is surely justified.

J. M. Cundy
Lewisham, London

REFERENCES

Radford, P., and Thurlow, A. C. (1979). Metallized plastic sheeting in prevention of hypothermia during surgery. *Br. J. Anaesth.*, **51**, 237.

Chambers, J. J., and Saha, A. K. (1979). Case report. Electrocution during anaesthesia. *Anaesthesia*, **17**, 173.

Sir,—There is no doubt that metallized plastic sheeting is used in several theatres in this country in an attempt to keep patients warm. Our trial was to assess the efficacy of this material; no protection from hypothermia was demonstrated.

Our advice from the D.H.S.S. Technical Department (personal communication) is that there is a slight but definite risk of burns caused by aberrant grounding of diathermy current if there is a fault in the earth lead of the diathermy equipment.

Since metallized plastic sheeting is neither effective in patients undergoing neurosurgery, nor safe for patients in conjunction with diathermy, we must conclude that this material has little place in the operating theatre.

Patrick Radford
A. C. Thurlow
Carshalton, Surrey

In view of the importance of Dr Cundy's remarks, the Editor invited Dr D. W. Hill to comment on this problem.

Sir,—It must first be stressed that it is a very serious matter for surgical diathermy equipment to be used with a fault on the plate electrode or its return lead. In the absence of a proper return path the radio frequency potential on the patient is likely to seek alternative paths back to earth either via a patient touching an earthed object or via capacity of a coupling to earth. When a properly attached plate electrode is in use one would not expect there to be a risk of burns arising from the use of the metallized plastic sheeting as the diathermy current would normally flow back to the diathermy set via the plate electrode.

Should there be a fault on the plate electrode and the plastic covering of the metallized sheet not be punctured, then it is reasonable to suppose that there would be a capacitive coupling of the radio frequency current back to earth. However, this would be a general distributed capacitant over the surface area of the patient covered by the sheeting and I would have thought the surface area through which the current would flow would be sufficiently large that there was not much risk of a burn occurring to the patient. If the plastic cover of the sheeting becomes punctured then there may be a risk of a localized burn if the surface area of the metallized layer exposed to the patient is small. However, it is quite likely that the sheet would puncture in more than one place and so there is less of a risk of a burn.

Without the benefit of having conducted some experiments, this argument has to be somewhat problematical. The manufacturer's literature supplied on the space rescue blanket says that it will keep people warm despite violent weather conditions such as snow and freezing temperatures. However, Dr Radford's letter indicates that in his trial the use of the space blanket did not give any protection from hypothermia.

Unfortunately I have no details of his tests, but assuming that his conclusion is correct, then clearly there is no point in recommending the use of these metallized blankets during surgery. This appears to be the over-riding consideration. I am doubtful whether the risk of a burn arising to the patient would be much greater if such a blanket was employed than would happen in any case if the plate electrode connection came open-circuited. It is not feasible to see that the use of the metallized blanket would substantially reduce any risk of burn to the patient.

If the performance of the blanket is poor in respect of its heat-loss properties then I think this is the end of the matter. I must stress the need to ensure that there is an adequate maintenance schedule for the surgical diathermy and its plate electrode.

It is essential to try to minimize the number of radio frequency burns which arise during surgery.

D. W. Hill
London

THE TOAD IN THE HOLE: AN HYPOTHESIS TO EXPLAIN THE ACTION OF ANAESTHETICS

Sir,—Any theory which attempts to account for the action of volatile general anaesthetic agents must explain these three phenomena. First, the nature of the state of general anaesthesia. Second, the vast variety of volatile general anaesthetic agents which are pharmacologically active. Third, the antagonism between the effects of general anaesthetics and those of increased atmospheric pressure.

The human central nervous system has 10^{10} neurones and 3.6×10^6 input axons. Each input will therefore react with about 3×10^3 neurones before finding an output. It is probable that vital activities like control of respiration or circulation involve circuits which have a small number of synapses in series and the higher activities such as consciousness involve circuits having a large number of synapses in series. It is also probable that general anaesthesia is a state in which the circuits involving large numbers of synapses in series are interrupted while the simpler circuits are unaffected. Thus consciousness is lost but the vital activities continue. A general anaesthetic will therefore be an agent which has a low probability of blocking a synapse, so that when a large number of synapses in series is affected the probability of interruption becomes high.

Many proteins have a structure in which one or more polypeptide chains are curled roughly into a ball having the polar groups pointing outwards and the non-polar groups directed inwards. The chain may enclose a central void which a volatile anaesthetic, being a small non-polar molecule, may enter. If a protein molecule of this nature is subjected to increased pressure one would expect it to become compressed so that the central void is reduced in volume; however, if the central void is already occupied by an anaesthetic, like a toad in the hole, the protein would be more resistant to compression.

When a patient receives a general anaesthetic a large number and variety of protein molecules will have their central voids occupied by the molecules of volatile anaesthetic agents. In the majority of cases their physiological activities are unaffected; however, there are grounds for concluding that the action of the acetylcholine receptor protein molecule is profoundly affected and that this action is responsible for the phenomenon of general anaesthesia. The receptor protein is a tetramer enclosing a central pore which is normally closed but which opens under the influence of acetylcholine or increased pressure to permit a flow of ions which depolarizes the neuronal cell membrane and generates an action potential. It is likely that, when the central pore opens, the central void of the receptor protein molecule is reduced in volume. The characteristics of this reaction, namely the dissociation constant of acetylcholine and its time constant, indicate that the energy required to compress the molecule must be quite small, so that it would be especially susceptible to the "toad in the hole" effect; in addition, at the correct dose a sufficient proportion of synapses would be blocked to cause general anaesthesia.

The central void, being of an irregular shape, can contain non-polar molecules of a large variety of shapes provided they do not exceed a certain size, and this may explain why such a large variety of volatile non-polar molecules can act as general anaesthetics. Most pharmacological actions involve attachment to a surface where the conformational conditions are specific; however, when a molecule is contained within a void, a greater variety of molecules may be admitted and retained.

It is difficult to determine with certainty to what extent the circulation of nerve impulses which may constitute the objective embodiment of consciousness is dependent on transmission across central cholinergic synapses. However, it is likely that the majority are cholinergic, but when they are not cholinergic it is possible that the receptor protein has to undertake an allosteric transformation which is also vulnerable to interference by the presence of an anaesthetic molecule in its central void. Although a great number and variety of proteins will be affected by non-polar molecules in this way, it would seem probable that the synaptic protein molecule is the most vulnerable in this context.

B. JAMES
Marlow, Bucks

PANCURONIUM PLASMA CLEARANCE AND AGE

Sir,—It is now widely accepted that age can influence drug disposition, and the report by McLeod, Hull and Watson (1979) of a reduced plasma clearance of pancuronium with increasing age is another example of age-dependent pharmacokinetics. Nevertheless, it seemed appropriate to compare these results with those of Somogyi (1978).

Thirty-eight patients aged 15–77 yr were studied; their weights were in the range 45–88 kg and all received general anaesthesia for elective surgery. They included patients given single ($n = 11$) and multiple ($n = 6$) bolus and infusion ($n = 21$) regimens of pancuronium and were all free from renal, hepatic and neuromuscular disorders. The anaesthetic technique, analysis of pancuronium and pharmacokinetic analysis have been described previously (Somogyi, Shanks and Triggs, 1978). The plasma clearance of pancuronium as a function of age is shown in figure 1.

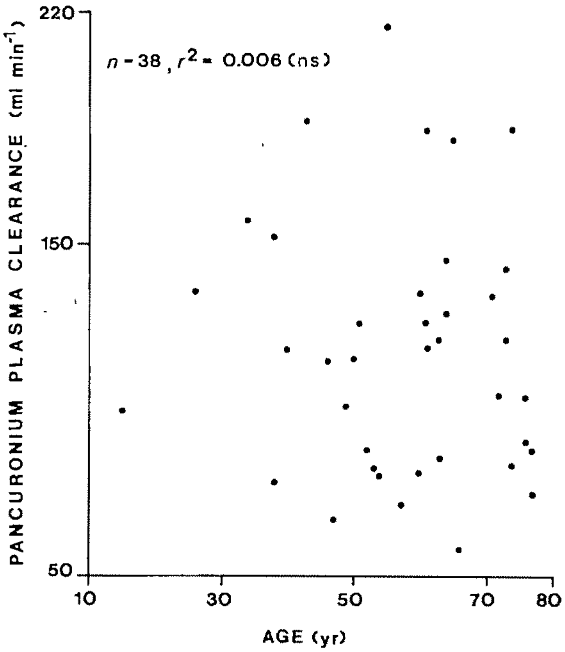


FIG. 1. Pancuronium plasma clearance as a function of age.

There was no statistically significant ($P > 0.05$) linear relationship between these two variables. The reasons for the differences between these results and those of McLeod and his co-workers are speculative, but it would appear that more detailed studies are required to investigate this and other aspects of the disposition of non-depolarizing muscle relaxants in surgical patients.

A. SOMOGYI
Bonn, Germany

REFERENCES

McLeod, K., Hull, C. J., and Watson, M. J. (1979). Effects of ageing on the pharmacokinetics of pancuronium. *Br. J. Anaesth.*, **51**, 435.

Somogyi, A. A. (1978). The clinical pharmacology of pancuronium bromide. Ph.D. Thesis, University of Sydney, Australia.

—— Shanks, C. A. and Triggs, E. J. (1978). Combined i.v. bolus and infusion of pancuronium bromide. *Br. J. Anaesth.*, **50**, 575.

Br. J. Anaesth. (1980), **52**, 361

BOOK REVIEWS

Topics in Anaesthesia and Intensive Care. By J. A. Thornton and C. J. Levy. Published by Henry Kimpton, London. Pp. 158; illustrated. Price £4.60.

Anaesthetics is now a small part of the undergraduate curriculum and it has been argued for some time that the chief purpose of student attachments to the clinical department is to gain experience in the care of the unconscious patient, in resuscitation and in the clinical appreciation of basic physiological functions. Thus it is inevitable that books for undergraduates have moved a long way from the old-fashioned, didactic "textbook of anaesthetics". The reviewer would query how far this trend should go. It may be that someone will write down so far that the undergraduate will cease to perceive anaesthesia as a subject at all.

This particular volume is entitled, "Topics . . ." and rightly so. The authors have provided a discursive commentary on general anaesthesia in about 80 pages and the slightly smaller rest of the book is concerned with nerve blocks and pain relief and the simplest basics of intensive therapy.

The book is well produced, is pleasant to handle and to read and is unusually free from typographical error. However, there are several flaws, occasionally frank errors, but more often causes to wonder whether a particular point is well or happily made. "Trichloroethylene cannot be used with a *vapouriser* containing soda lime." "It is more usual to monitor blood pressure and heart rate constantly and *equate* these with the vasodilatation of the skin." The preparations for endotracheal intubation do not apparently include the administration of oxygen. There is a peculiar bodily transposition in the manoeuvre " . . . the head should be extended at the neck and slightly flexed at the atlanto-occipital joint." Is the normal range of dosage really the same 10–20 mg for both morphine and papaveretum? Is it right to illustrate the induction of anaesthesia with thiopentone by photographs of a 20-ml syringe containing an air bubble being used in the antecubital fossa? Is the text sufficiently strong—". . . great care is necessary to avoid an intra-arterial injection or damage to the median nerve, and for this reason the lateral veins *are the ones of choice*"?

There are some interesting diagrams of the mechanisms of various physiological states with many arrowed pathways. These certainly make a number of points and stimulate thought, but one wonders why "fractured ribs" is connected by a direct arrow to "pain" and to "pneumothorax", but only indirectly to "paradoxical ventilation" via "impaired mechanics ventilation". The difficulty of constructing such diagrams satisfactorily is shown by the fact that, in figure 18, "reduced cardiac output" leads to "reduced availability of oxygen" and thence to "reduced mixed venous oxygen content", whereas in figure 21 the first and third of these terms each lead, quite independently, to the second.

This book covers the more important aspects of the work of an anaesthetist, but it has serious faults and does not do its authors justice.

E. A. Cooper

Development of Volatile Inhalational Anaesthetics, Monographs in Anaesthesiology, Volume 6. Edited by A. B. Dobkin. Published by Excerpta Medica, Amsterdam, Oxford, New York. Pp. 370; illustrated; indexed. Price $70.25.

Although this book is a multi-author publication it is very much the work of its editor, Professor A. B. Dobkin, who unfortunately died during the preparation of the work. This may account for the lack of recent information in some of the chapters. Professor Dobkin was well known for his original work on the introduction of many of the volatile anaesthetics and in this volume he has contributed chapters on halothane, enflurane and isoflurane (Forane), on the toxicity of inhalation anaesthetics and on vaporizers. An historical contribution on diethyl ether, chloroform, ethyl chloride, ethylene, trichloroethylene, and on agents about which little has been written in the British anaesthetic literature, such as ethyl vinyl ether, fluroxene, and halopropane and other propane derivatives, are well reviewed by Wilson and Fabian. A chapter on biotransformation of inhalation anaesthetics, by Van Dyke and a section on methoxyflurane by Van Poznak, completes the line-up.

The book is a brave attempt to gather together in one place all the relevant information about the commonly used and potential volatile inhalation anaesthetics. In the main, the attempt has been successful. However, recent advances in the metabolism of volatile anaesthetics are barely covered by Van Dyke and this illustrates the time lag between the writing of the chapters and eventual publication. Although organ toxicity is covered briefly, there is only passing reference to the problems associated with contamination of the atmosphere by volatile anaesthetics. This latter consideration must be an important factor in the development of new volatile anaesthetic agents.

As a repository of fact and information concerning volatile anaesthetics this book can be recommended. However, its cost may inhibit the individual anaesthetist from purchasing a copy and it seems a more appropriate volume for the departmental library shelf.

Leo Strunin

Developments in Clinical Nutrition. (Proceedings of a Symposium at the Royal College of Physicians, London, October 20, 1978.) Edited by I. D. A. Johnston and H. A. Lee. Published by MCS Consultants. Pp. 116; indexed; illustrated. Price £3.50.

One of the real advances of the past decade has been the increasing awareness of the importance of adequate nutrition in general patient care. While not minimizing in any way the role of parenteral nutrition, there is no doubt that, wherever possible, patients should be fed by the gastrointestinal tract. In recent times, the introduction of fine-bore feeding tubes and the availability of sterile balanced liquid diets has revolutionized tube feeding and has made "enteral nutrition" a simple, safe and efficient procedure.

This small book presents the proceedings of a timely two-session symposium on the importance of enteral feeding and packs a wealth of good sense into its 116 pages. The layout is along conventional lines with the opening papers describing the rationale and physiological background. These are followed by a section on the metabolic and practical aspects of nutritional support, methods of patient assessment and nutrition in specialized fields. There is also a valuable contribution by Dr M. W. Casewell on the worrying problem of bacterial contamination of conventionally prepared nasogastric feeds. Speakers' references are published in full, as are the lively panel discussions which concluded both sessions.

Inevitably there is some variation in the standard of papers presented. Nevertheless, the overall impression is that this was a useful symposium and the published proceedings should prove valuable to clinicians who have their patients' nutritional welfare at heart.

Winifred E. I. Finlay

Principles and Practice of Blood-gas Analysis. By A. P. Adams and C. E. W. Hahn. Published by Franklin Scientific Projects Ltd, London. Pp. 95; illustrated. Price £8.

This book, written by two acknowledged experts in the field of blood-gas and acid–base analysis, is perfect proof of the adage that deep understanding of a subject is needed to explain complex and difficult concepts in simple, logical and easily grasped terms. Without resort to excessive simplification the authors describe, systematically and with great clarity, the underlying principles of blood-gas analysis, the methods of measurement and the interpretation of the results obtained.

The book is in three sections. The first four chapters deal with the basic physics and physiology of oxygen and carbon dioxide homeostasis and transport. Whilst most of the subject matter here can be found in standard textbooks, the basic principles necessary for understanding the subject matter of the book are comprehensibly and clearly explained. The next two chapters consider acid–base balance. The differences between the *in vivo* and *in vitro* approaches are lucidly explained. The use of standard nomograms is described, but more stress is placed on the beside "*in vivo*" approach to the diagnosis of acid–base disorders. The authors emphasize and explain why one should not merely look at results from a blood-gas analyser, but also take into consideration factors such as the history, plasma electrolyte concentrations and the anion gap in coming to a final diagnosis.

The last six chapters are concerned with the methodology of blood-gas and acid–base measurements. Clear explanations of the working principles of the relevant electrode systems are given. There is an excellent chapter on quality control and useful sections on the measurement of oxygen content and saturation, haemoglobin and *in vivo* blood-gas analysis.

The book is copiously illustrated and virtually all the graphs and line drawings are coloured. Whilst a few of the illustrations (for instance those showing the two-syringe method for oxygen content determination) seem unnecessary, most are perfectly complementary to the text. The only major failing of the book is the lack of an index. Despite this, the book can be wholeheartedly recommended to the tyro, practitioner, teacher and expert.

C. M. Conway

A Practice of Anaesthesia, 4th edn. Edited by H. C. Churchill Davidson. Published (1978) by Lloyd Luke, London. Pp. 1487; illustrated; indexed. Price £26.

For one who was just (some say comfortably) in time to be reared on the first edition of this book, the appearance of the fourth edition is a welcome sign of continuity and hope in a specialty that surely must be repleat with monographs of increasing complexity and decreasing scope such that ordinary folk are encouraged to believe that no mind can encompass all that is to be known. Perhaps too many monographers cannot write, or it may be that too many publishers are in competition, but whatever the reason the problem shows no sign of abating. The first criticism that could be levelled at *A Practice of Anaesthesia*—that there is no need for a textbook of anaesthesia—is in my view ridiculous; the need has never been greater. The problem is, however, to decide what does and does not qualify for inclusion in the core of knowledge. For a book with the important and valuable tradition of this one, Dr Churchill Davidson (now sadly without the participation of the founder, Dr Wylie) has taken council of 18 associate editors, all within a bus-ride of his own doorstep; all of this I applaud. What is perhaps more contentious is the manner in which they have approached their task, because I did not always find that they had consistently produced (in the words of the preface) "a balanced viewpoint of a particular topic". One hesitates in giving examples because they occur in almost every chapter and none is outstandingly bad. In the very detailed chapter on pulmonary ventilation, however, the description of anaesthetic breathing systems is traditional and brief; a substantial proportion is devoted to soda-lime, but relatively little to the place, if any, of the circle system in contemporary practice.

The chapter on hyperbaric physiology in medicine is excellent in its own right. Within this book, however, the detail seems perhaps a little excessive and one wonders about the value of the photographs of the Russian installations. I will let others judge if less than two pages on contamination of operating room environments is appropriate; it is a fact that the citation of the published literature is oblique, there being no reference to the European publications at all.

In spite of these blemishes, the new edition of this book makes good reading. It is not and is not intended to be a major source of reference in anaesthesia, but if I were starting my education in the specialty all over again I believe that the fourth edition would serve me as well as I believe its predecessors have done.

Alastair A. Spence

Printed in Great Britain by John Wright and Sons Ltd, at The Stonebridge Press, Bristol BS4 5NU

© Macmillan Journals Ltd 1980

THE HOWORTH ACTIVE SCAVENGING SYSTEM FOR ANAESTHETIC GAS POLLUTION

The Howorth anaesthetic gas scavenging system is an active system designed specifically to reduce air pollution by anaesthetic gases to well below the maximum levels recommended by N.I.O.S.H. in the U.S.A. and by the British Association of Anaesthetists in the U.K. The system complies with the principles of D.H.H.S. Circular HC(76)38.

SYSTEM CHARACTERISTICS

High Volume, Low Pressure

The high volume ensures high dilution of gases and all moisture, thus avoiding explosion risk and any condensation within the ducts.

No excessive or dangerous suction pressure can be exerted on the anaesthetic machine circuits.

There is no imbalance of pressure if only one extract point is being used on a multi-point system.

Versatility of Function

This system is applicable to any anaesthetic circuit and any type of ventilator also, with an adaptor, for dentistry and pediatrics.

Break Point Connections

These are designed to limit the suction pressure on the machine circuits to the required and recommended limit of 0.5 cm/H_2O.

They cannot be occluded accidentally.

They are compatible with 18 mm, 22 mm or 30 mm extract hose and they are capable of exhausting peak flows of up to 300 litres per minute.

Multi-Purposes Application

The system is designed to cope with extracts from anaesthetic rooms and also to exhaust the patient's breath in recovery rooms.

Versatility of Layout Design

The system can be adapted to scavenge simultaneously, for example, four anaesthetic machine points, or three or four recovery room points, or combinations of machine and recovery room points.

Each extract point is fitted with a self-closing valve which enables alternative extract points to be installed on the same fan system.

Inbuilt Safety Factors

A failure light on the control and indicating panels is activated by an air flow sensor fitted to the fan.

The fan motor is outside the air stream, and the fan blades are of non-ferrous material.

Should the fan motor fail, the system can still operate, as a temporary measure, as a passive system without adversely affecting the anaesthetic circuits.

Typical Test Results

Hospital 'A'

Operating Theatre—	no scavenging: 600–1000 ppm N_2O
	passive system: 230–300 ppm N_2O
	Howorth system: 0–3 ppm N_2O
Comment:	The 3 ppm were traced to leaks in the anaesthetic circuitry.

Hospital 'B'

Operating Theatre—	no scavenging: 800–1000 ppm N_2O
	Howorth system: 0–6 ppm N_2O
Comment:	The 6 ppm were traced to a leaking cuff on the endotracheal tube.

We should be pleased to offer any further information on request.

HOWORTH SURGICAIR

Lorne Street, Farnworth, Bolton. Tel: 0204-71131 Telex: 635242

Design Council Award 1977

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 3 *Published monthly* MARCH 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27.50, Airmail £50 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.

CONTENTS

PAGE

EDITORIAL 245

CLINICAL INVESTIGATION

Observations on extradural morphine analgesia in various pain conditions 247
F. Magora, D. Olshwang, D. Eimerl, J. Shorr, R. Katzenelson, S. Cotev and J. T. Davidson

Posterior intercostal nerve block for pain relief after cholecystectomy. *Anatomical basis and efficacy* 253
J. F. Nunn and G. Slavin

Constrictive effect of pancuronium on capacitance vessels 261
C. Lee, E. Yang and M. Lippmann

Ventilatory depression of the newborn of women reveiving pethidine or pentazocine. *A double-blind comparative trial* 265
S. O. Refstad and E. Lindbæk

Ventilatory management of neonates undergoing surgery. *A review of the first 3 years' experience in a neonatal surgical intensive care unit* .. 273
A. M. Mackersie, D. J. Hatch and G. M. Farnsworth

Behaviour of unsedated children in the anaesthetic room 279
D. G. Beeby and J. O. Morgan Hughes

Comparison of oral triclofos, diazepam and flunitrazepam as premedicants in children undergoing otolaryngological surgery 283
L. Lindgren, L. Saarnivaara and J.-J. Himberg

Comparative study of atropine and glycopyrrolate on suxamethonium-induced changes in cardiac rate and rhythm 291
D. A. Cozanitis, J. W. Dundee and M. M. Khan

A double-blind comparison of meptazinol with pethidine in postoperative pain 295
A. Hedges, P. Turner and J. Wadsworth

Fine screen filtration of banked blood: effect on red cell survival 299
J. D. Browning, I. C. M. Gray and I. McA. Ledingham

EXPERIMENTAL

Plasma concentrations of noradrenaline and adrenaline and plasma renin activity during extradural blockade in dogs 305
B. Stanek, M. Schwarz, M. Zimpfer and G. Raberger

PAGE

Inhibition of neuronal uptake of noradrenaline in the isolated perfused rat heart by pancuronium and its homologues, Org. 6368, Org. 7268 and NC 45 313
P. J. Salt, P. K. Barnes and C. M. Conway

Effects of temperature, adenosine triphosphate and magnesium concentrations on the contraction of actomyosin isolated from halothane-sensitive and -insensitive German Landrace pigs 319
R. A. Green, G. Mitchell and J. J. A. Heffron

The nature of gentamicin-induced neuromuscular block 325
T. A. Torda

Time-course of formation of volatile reductive metabolites of halothane in humans and an animal model 331
G. K. Gourlay, J. F. Adams, M. J. Cousins and J. H. Sharp

Circulatory responses of the dog to acute, isovolumic anaemia in the presence of high-grade adrenergic beta-receptor blockade 337
T. N. S. Clarke, P. Foëx, J. G. Roberts, C. A. Saner and M. J. Bennett

Effect of anaesthesia with nitrous oxide in oxygen and fentanyl on renal function in the artificially ventilated dog 343
J. M. Hunter, R. S. Jones and J. E. Utting

Preliminary *in vitro* study of diazepam and droperidol on oestrus rat uterus 349
A. A. Khan

CORRESPONDENCE

Anaphylactoid type adverse responses 355
Equations 356
Enfluratec vaporizer 356
Analgesic action of extradural fentanyl 357
Metallized plastic sheeting 359
The Toad in the Hole: an hypothesis to explain the action of anaesthetics 359
Pancuronium plasma clearance and age 360

BOOK REVIEWS

Topics in Anaesthesia and Intensive Care 361
Development of Volatile Inhalational Anaesthetics .. 361
Developments in Clinical Nutrition 361
Principles and Practice of Blood-gas Analysis .. 362
Local Analgesia 362
A Practice of Anaesthesia 362

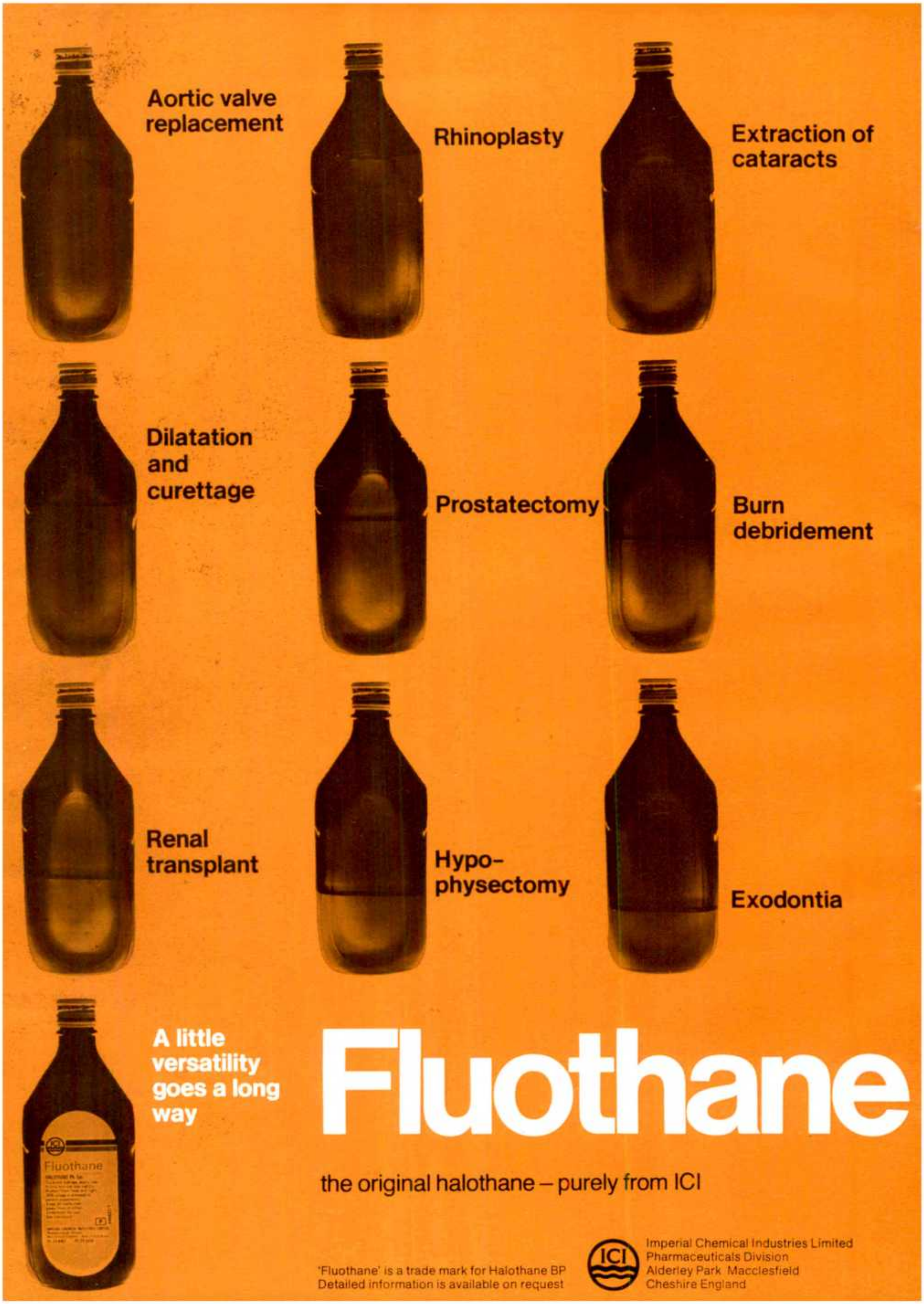
EDITORIAL BOARD page ii

MACMILLAN JOURNALS LTD, 4 LITTLE ESSEX STREET, LONDON WC2R 3LF

Volume 52, No.4 April 1980

British Journal of Anaesthesia

Editor of General Issues: A. A. Spence



A little versatility goes a long way

Fluothane

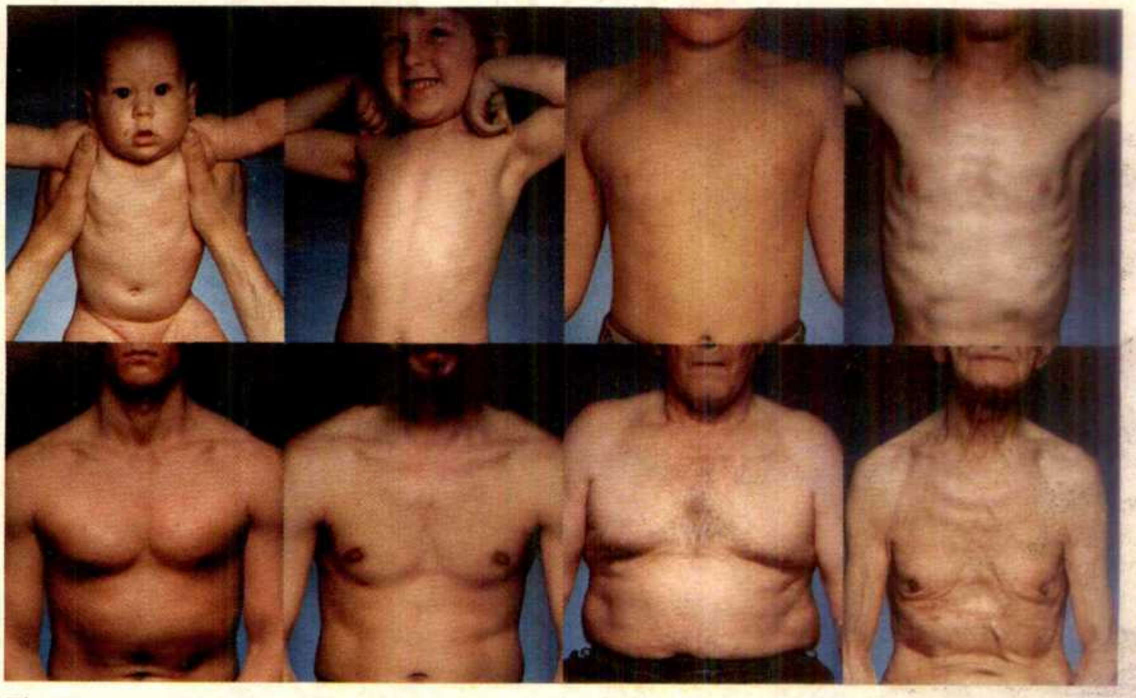
the original halothane – purely from ICI

'Fluothane' is a trade mark for Halothane BP
Detailed information is available on request

Imperial Chemical Industries Limited
Pharmaceuticals Division
Alderley Park Macclesfield
Cheshire England

Acc
19.9.80.

The Engström 300 automatically adapts to any patient.



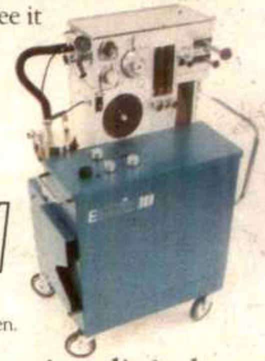
The Engström 300 is designed so the ratio between the active insufflation phase and the plateau phase, where "slow" alveoli get time to fill, can vary from breath to breath. This way, it automatically compensates for changes in the lung mechanics of any patient, regardless of size.

It is an all-purpose respirator. Models are available for both adults and children, and accessories make it easily adaptable for intensive care or anaesthesia.

The Engström 300 can operate as a completely self-contained unit. It can carry its own supplies of gas, and has its own built-in driving compressor. Just wheel it to where you need it, plug it into the mains, and it's ready to work.

All parts are designed to withstand much more than their share of hard use. Preventative maintenance and repair is done with simple tools.

These are some of the reasons why hospitals all over the world swear by their Engströms. We would like you to see for yourself. Contact your nearest Engström representative for more information, and you'll get our new brochure. Or, if you would like to see it demonstrated on your own ground, he will arrange an appointment at your convenience.



ENGSTRÖM

Engström Medical AB,
Box 1295, S-171 25 Solna, Sweden.

Engström 300 - the self-contained, all-purpose respirator for routine clinical use.

EDITORIAL BOARD

Editor of General Issues

A. A. SPENCE, *Reader, University Department of Anaesthesia, Western Infirmary, Glasgow*

Editor of Postgraduate Educational Issues

J. NORMAN, *Professor of Anaesthetics, The General Hospital, Tremona Road, Southampton SO9 4XY*

C. M. CONWAY, *Professor of Anaesthesia, Westminster Hospital, London*
E. A. COOPER, *Professor of Anaesthesia, University of Newcastle upon Tyne; Honorary Consultant Anaesthetist, Newcastle University Hospitals*
J. W. DUNDEE, *Professor of Anaesthesia, Queen's University of Belfast*
F. R. ELLIS, *Reader in Anaesthesia, University of Leeds*
W. FITCH (Assistant Editor), *Senior Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*
G. M. HALL, *Senior Lecturer in Anaesthetics, University of London, Royal Postgraduate Medical School*
C. J. HULL, *Senior Lecturer in Anaesthesia, University of Newcastle*
A. R. HUNTER (Chairman), *Professor of Anaesthesia, University of Manchester*
D. G. MCDOWALL, *Professor of Anaesthesia, University of Leeds*
W. W. MAPLESON, *Professor of the Physics of Anaesthesia, Welsh National School of Medicine, University of Wales*
J. F. NUNN, *Head of Division of Anaesthesia, Clinical Research Centre, Harrow; Honorary Consultant Anaesthetist, Northwick Park Hospital*
J. P. PAYNE, *British Oxygen Research Professor of Anaesthetics, Royal College of Surgeons of England*
C. PRYS-ROBERTS, *Professor of Anaesthetics, University of Bristol*
J. E. RIDING (Hon. Treasurer), *Consultant Anaesthetist, United Liverpool Hospitals; Honorary Lecturer in the Department of Anaesthesia, University of Liverpool*
J. G. ROBSON, C.B.E. *Professor of Anaesthetics, University of London, Royal Postgraduate Medical School*
D. B. SCOTT, *Consultant Anaesthetist, Royal Infirmary, Edinburgh*
G. SMITH, *Professor of Anaesthesia, The General Hospital, Leicester*
M. K. SYKES, *Professor of Clinical Anaesthesia, Royal Postgraduate Medical School, London*

Editorial Assistants

KIRSTEEN M. S. DEWAR, *Consultant Anaesthetist, Western Infirmary, Glasgow*
G. N. C. KENNY, *Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*

Papers for publication and all editorial communications should be addressed to the Editor, University of Glasgow, Department of Anaesthesia, Western Infirmary, Glasgow G11 6NT; business communications to the publishers: Scientific & Medical Division, Macmillan Publishers Ltd, Houndmills, Basingstoke, Hampshire RG21 2XS.
Published monthly. Annual subscriptions: U.K. £22·50, U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27·50, Airmail £50; (or equivalent in any other currency). ISSN 0007–0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.
Overseas subscribers may make payments into U.K. Post Office Giro Account No. 519 2455. Full details must accompany the payment.
Second Class Postage Paid New York, N.Y. U.S. Mailing Agent: Expediters of the Printed Word, Ltd, PO Box 1305, Long Island City, N.Y. 11101.

All enquiries concerning advertising should be addressed to Advertisement Department, Macmillan Journals Ltd, 3 Dyers Buildings, Holborn, EC1N 2NR (Telephone 01-831 6901).

© Copyright: Macmillan Journals Ltd, 1980.

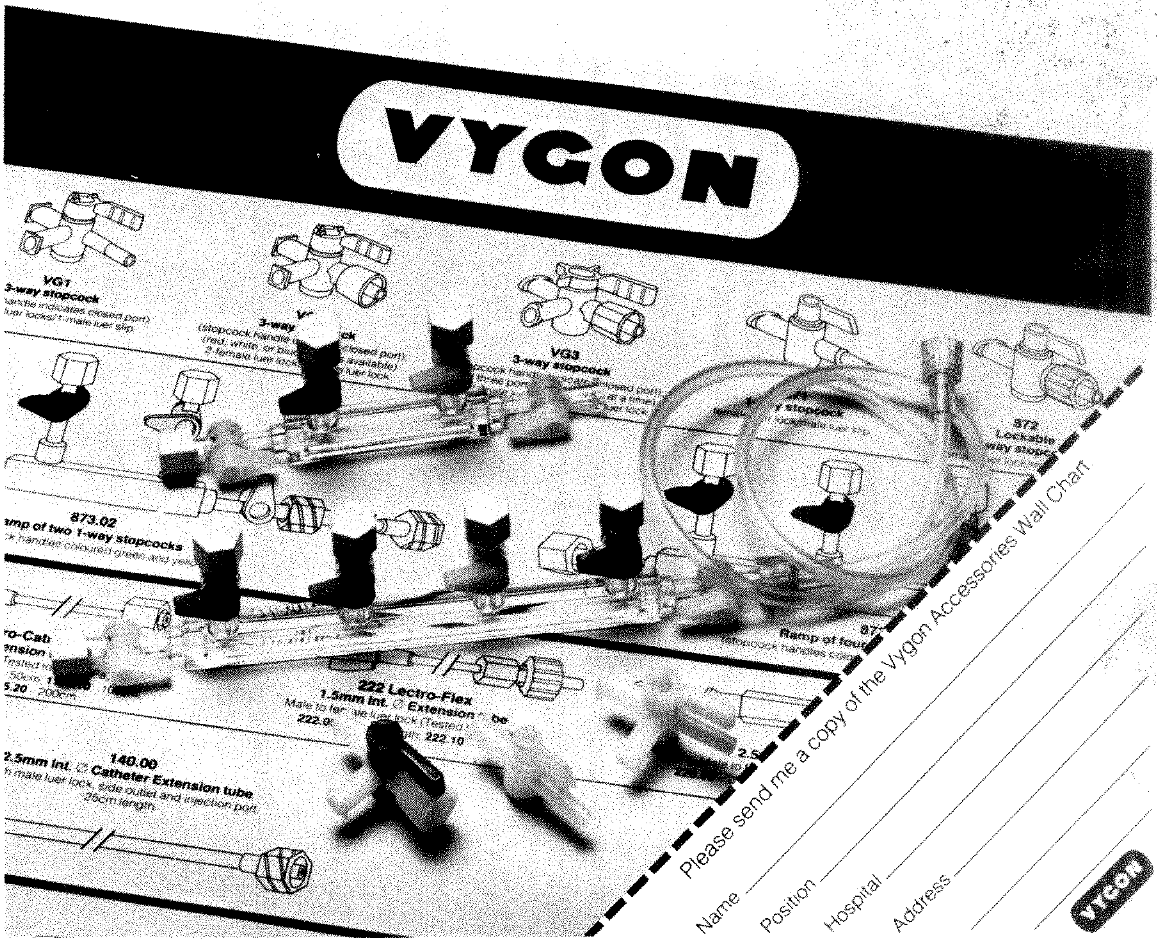
Registered Office: 4 Little Essex Street, London WC2R 3LF

Are 'traffic lights' holding you up?

Not if you are using Vygon 'traffic lights' – precision-built ramps of 2 or 4 one-way stopcocks, each line colour coded for ready identification. Vygon 'traffic lights' and other stopcocks in the Vygon range are supplied sterile, individually packed.

Vygon offers a comprehensive range of accessories for intravenous therapy and many other procedures; quality items designed to meet the most demanding requirements.

Vygon now offers for your convenience a fully illustrated Accessories Wall Chart, obtainable by completing the coupon below and sending it to:
Vygon (UK) Limited,
Bridge Road, Cirencester,
Gloucestershire GL7 1PT
Telephone: Cirencester (0285) 67051


VYGON
VG1
3-way stopcock
VG3
3-way stopcock
873.02
Ramp of two 1-way stopcocks
222 Lectro-Flex
1.5mm Int. ∅ Extension tube
140.00
2.5mm Int. ∅ Catheter Extension tube
872
Lockable
Ramp of four

Please send me a copy of the Vygon Accessories Wall Chart

Name

Position

Hospital

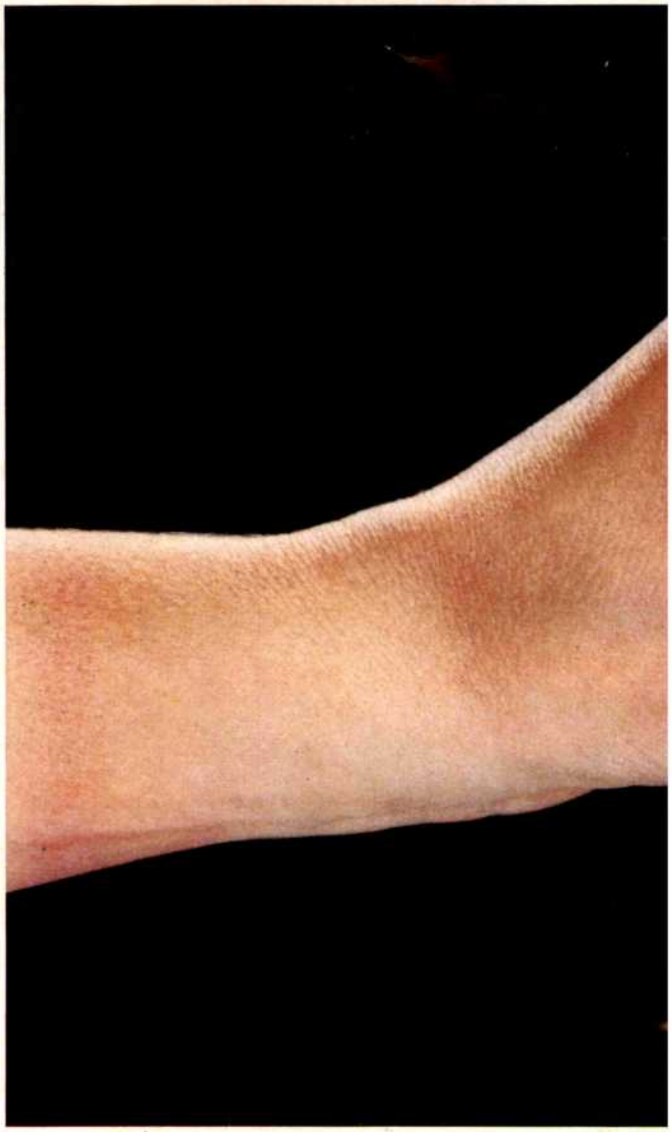
Address

VYGON

…or any other common blood gases. To get this much data on so many blood gases any other way, would need a whole programme of blood sampling. A time consuming and traumatic process.

Now all you need is the new Medishield Multi-gas Transcutaneous Probe. A simple, low-cost accessory to our Multi-gas Monitor MS2. Because it uses mass spectrometry, no common blood gas is outside its range. It can even examine up to four gases simultaneously.

Multi-gas
Monitor
MS2



And because of the exceptionally 'clean' signal achieved by the MS2, minute samples of gas are processable. Which is why we only need 0·5cm² of skin. It's the ideal system for intensive care and anaesthesia.

It's also remarkably uncomplicated in construction – as easy to apply as an ECG electrode; re-usable as often as necessary, but low-cost enough to be treated as disposable at the end of a patient programme.

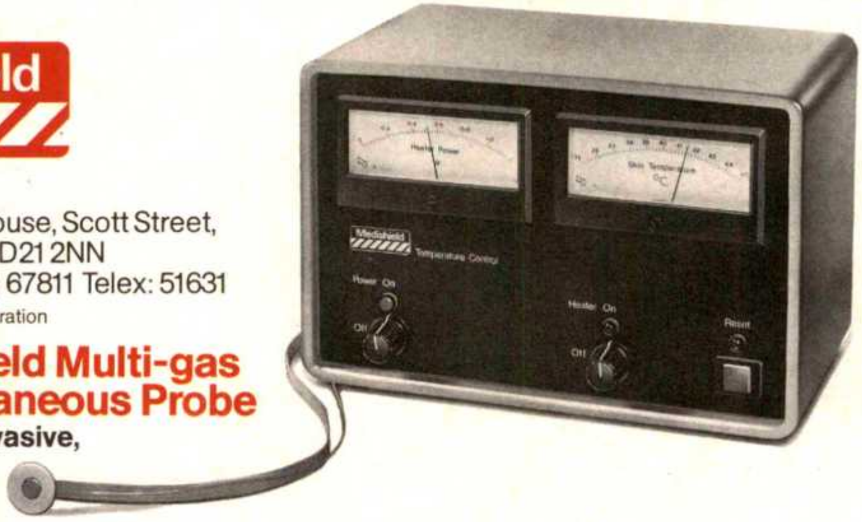
Get the full facts on the probe now. It could transform your approach to blood gas sampling.

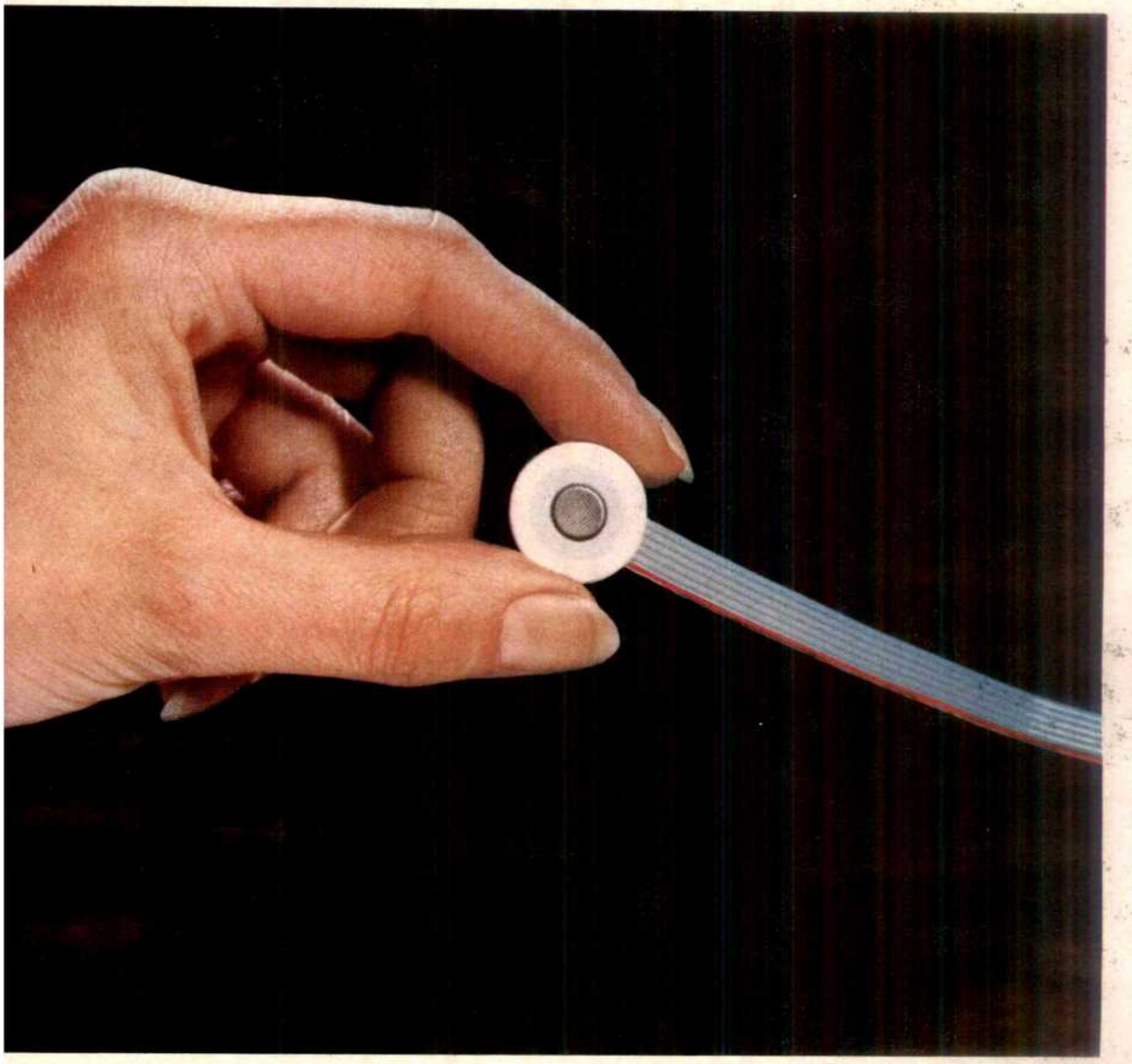
Medishield

Cyprane
New Devonshire House, Scott Street,
Keighley, W Yorks BD21 2NN
Tel: Keighley (0535) 67811 Telex: 51631
Part of the Medishield Corporation

The Medishield Multi-gas Transcutaneous Probe

The first non-invasive, multi-gas alternative





Probe shown actual size

Give us
0·5cm^2 of skin.
We'll give you tcPO_2, tcPCO_2,
tcPN_2O, tcPN_2, tcPHe...

DALHOUSIE UNIVERSITY

Department of Anaesthesia

CONSULTANT ANAESTHETIST

A vacancy exists for a consultant or staff anaesthetist in the Department of Anaesthesia, Dalhousie University, Halifax, Nova Scotia. The affiliated teaching hospitals comprise the Victoria General Hospital, the Halifax Infirmary and Camp Hill Hospital. In addition to clinical responsibilities, the successful applicant will be expected to become involved in both undergraduate and postgraduate teaching. An interest in Regional Analgesia, Pain Therapy or Intensive Care will be advantageous but not essential. A higher qualification in Anaesthesia is essential.

Applicants should submit a full curriculum vitae together with the names and addresses of three referees to:

Chairman
Department of Anaesthesia
Victoria General Hospital
Halifax, Nova Scotia
B3H 2Y9

University of Salford

Refresher Course for the Diploma in Anaesthetics
14–19 April 1980

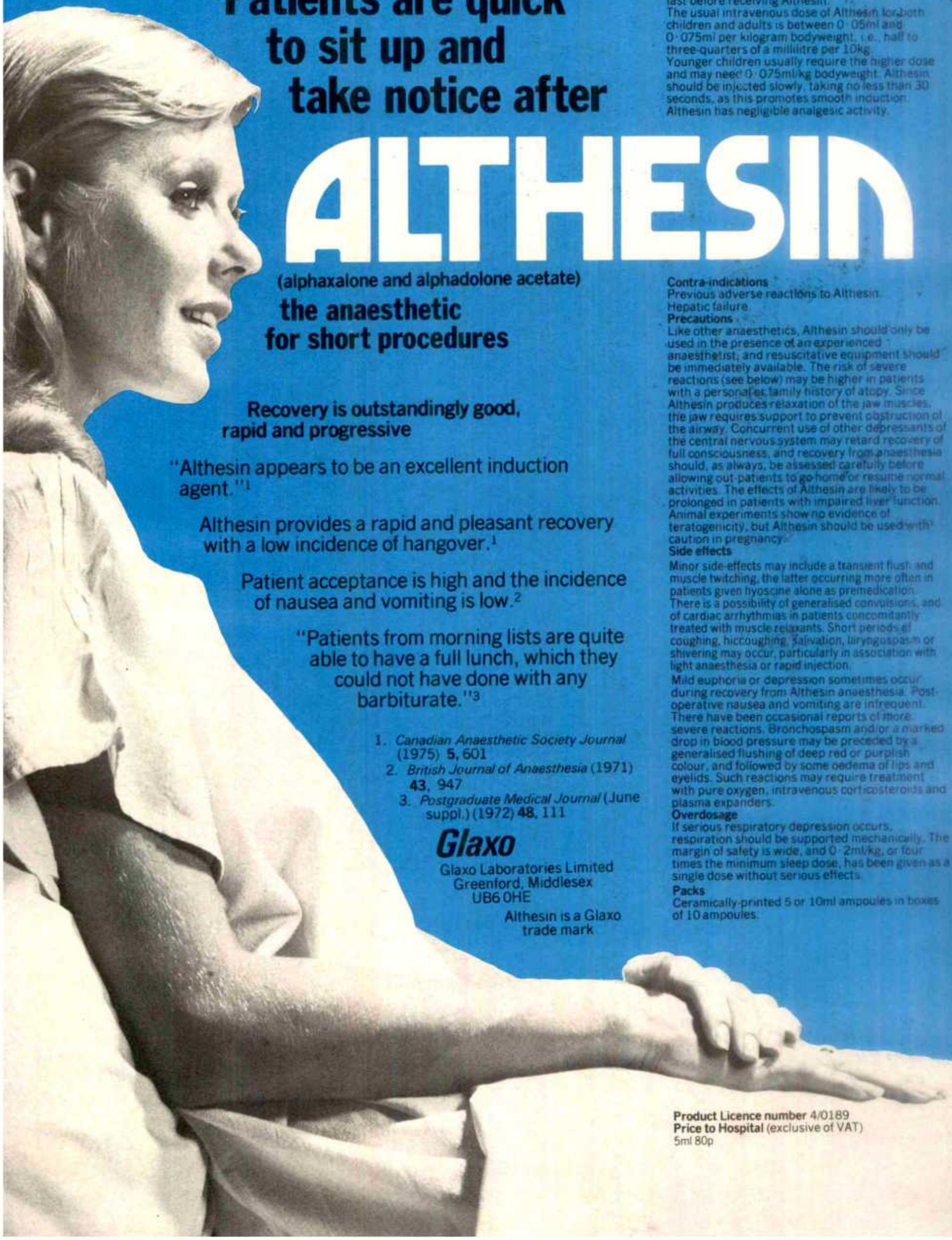
Intended to assist candidates preparing for the Diploma in Anaesthetics

Course Organiser: Dr P. Morris
Consultant Anaesthetist
Royal Manchester Children's Hospital

◆

Further details from: The Administrative Assistant (Short Courses)
Room 110
Registrar's Department
University of Salford
SALFORD M5 4WT

Telephone: 061-736 5843, extension 449



Patients are quick to sit up and take notice after

ALTHESIN

(alphaxalone and alphadolone acetate)

the anaesthetic for short procedures

Recovery is outstandingly good, rapid and progressive

"Althesin appears to be an excellent induction agent."[1]

Althesin provides a rapid and pleasant recovery with a low incidence of hangover.[1]

Patient acceptance is high and the incidence of nausea and vomiting is low.[2]

"Patients from morning lists are quite able to have a full lunch, which they could not have done with any barbiturate."[3]

1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

Glaxo

Glaxo Laboratories Limited
Greenford, Middlesex
UB6 0HE

Althesin is a Glaxo trade mark

Induction of anaesthesia
Maintenance of anaesthesia
Experience is insufficient at present to advocate use of Althesin in infants under one year, in patients with hepatic dysfunction, and for maintenance of anaesthesia in obstetrics.

Dosage and administration

As usual, it is recommended that patients should fast before receiving Althesin.
The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e., half to three-quarters of a millilitre per 10kg.
Younger children usually require the higher dose and may need 0·075ml/kg bodyweight. Althesin should be injected slowly, taking no less than 30 seconds, as this promotes smooth induction.
Althesin has negligible analgesic activity.

Contra-indications

Previous adverse reactions to Althesin
Hepatic failure

Precautions

Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants of the central nervous system may retard recovery of full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume normal activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects

Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, and of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post-operative nausea and vomiting are infrequent. There have been occasional reports of more severe reactions. Bronchospasm and/or a marked drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids and plasma expanders.

Overdosage

If serious respiratory depression occurs, respiration should be supported mechanically. The margin of safety is wide, and 0·2ml/kg, or four times the minimum sleep dose, has been given as a single dose without serious effects.

Packs

Ceramically-printed 5 or 10ml ampoules in boxes of 10 ampoules.

Product Licence number 4/0189
Price to Hospital (exclusive of VAT)
5ml 80p

SIEMENS

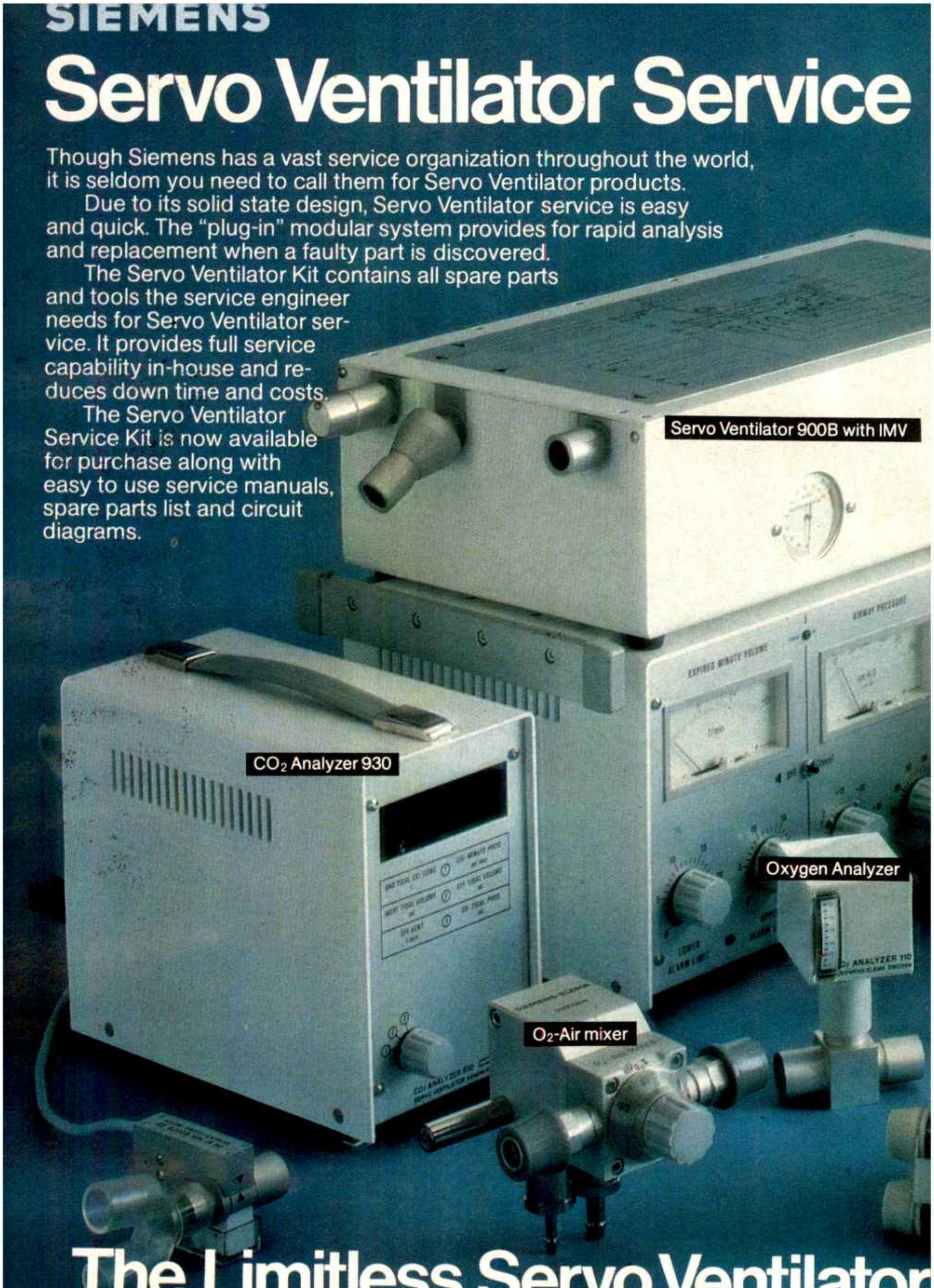
Servo Ventilator Service

Though Siemens has a vast service organization throughout the world, it is seldom you need to call them for Servo Ventilator products.

Due to its solid state design, Servo Ventilator service is easy and quick. The "plug-in" modular system provides for rapid analysis and replacement when a faulty part is discovered.

The Servo Ventilator Kit contains all spare parts and tools the service engineer needs for Servo Ventilator service. It provides full service capability in-house and reduces down time and costs.

The Servo Ventilator Service Kit is now available for purchase along with easy to use service manuals, spare parts list and circuit diagrams.



The Limitless Servo Ventilator

Please write for additional information or contact

SIEMENS-ELEMA
Siemens Limited, Medical Group
Electromedical Division
Siemens House, Windmill Road
Sunbury-on-Thames, Middlesex TW16 7HS
Telephone: (0327) 85691
For countries outside Great Britain:
Siemens-Elema AB, Ventilator Division
S-171 95 Solna, Sweden

System.

British Council Medical Courses

Recent Advances in Obstetrics and Gynaecology

21 September — 3 October 1980 in London

The Director of Studies will be Dr M de Swiet, Academic Sub-Dean, in association with Professor Sir John Dewhurst and Mr G V P Chamberlain of the Institute of Obstetrics and Gynaecology (University of London), Queen Charlotte's Maternity Hospital where the course will be based. The aim of the course is to present and discuss such recent advances in obstetrics and gynaecology in the United Kingdom as prenatal diagnosis and in monitoring the fetus both before and during labour. In gynaecology the emphasis has changed to gynaecological endocrinology in such cases as infertility and hirsutism but fertility research has also benefited from work in male fertility, tubal micro-surgery and extra-corporeal fertilisation. It is expected that the participants to the course will be able to contribute their own knowledge and opinions and ample time will be reserved for discussion. The course is intended for Specialist obstetricians and gynaecologists in hospital practice with at least five years experience.
There are vacancies for 50 members.
Fee including demi-pension accommodation £520.
Please apply by 30 April 1980.

Acute Injury — Clinical Management, Pathophysiology and Biochemistry

21 September — 3 October 1980 in Glasgow — London

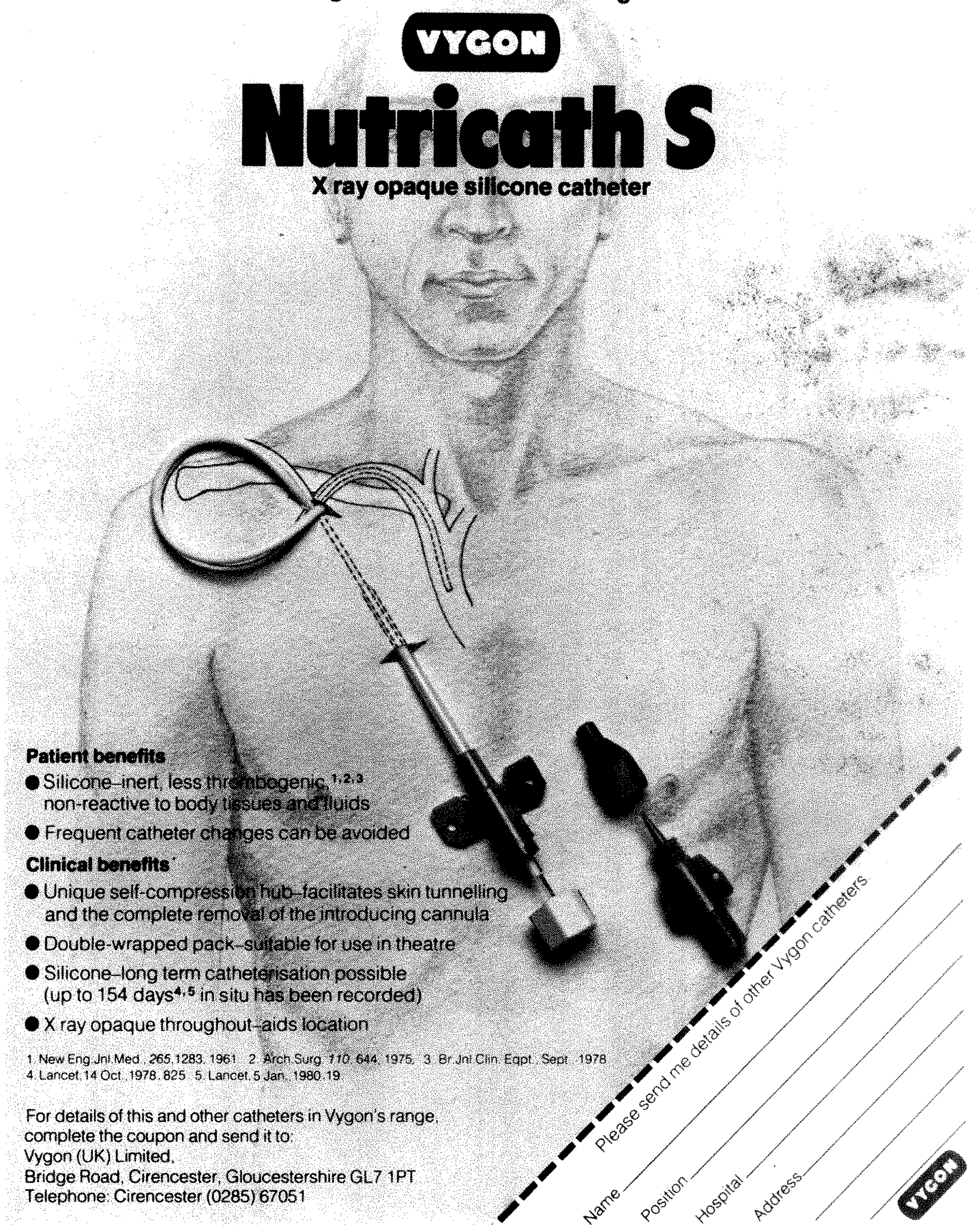
During this two week interdisciplinary course emphasis will be placed on the acute phase of injury of both surgical and traumatic origin but the common complications of sepsis and organ failure will also be covered. Practical problems of clinical management will be presented including advances in the nutritional aspects of the later phase of injury. Ample opportunity for active participation in discussion will be available at all sessions. The Directors of Studies will be Dr I McA Ledingham of the University Department of Surgery, Western Infirmary, Glasgow and Professor R G Clark of the Clinical Sciences Centre, Northern General Hospital, Sheffield. Members of the course will have an opportunity to visit a number of leading teaching hospitals and University Institutes in Glasgow and London. This course is intended for clinicians with an active interest in care of the acutely injured patient.
There are vacancies for 30 members.
Fee including full pension accommodation in Glasgow and demi-pension London £560.
Please apply by 2 May 1980.

Proposed Course

Advanced Paedodontics

8 — 20 March 1981 London and Newcastle
Director of Studies Professor G B Winters

Further information and application forms are available from local overseas Representatives of the British Council or from the Director, Courses Department, The British Council, 65 Davies Street, London W1Y 2AA, Britain.



For standard intravenous therapy and parenteral nutrition there are good reasons for choosing

VYGON

Nutricath S

X ray opaque silicone catheter

Patient benefits

- Silicone–inert, less thrombogenic,[1,2,3] non-reactive to body tissues and fluids
- Frequent catheter changes can be avoided

Clinical benefits

- Unique self-compression hub–facilitates skin tunnelling and the complete removal of the introducing cannula
- Double-wrapped pack–suitable for use in theatre
- Silicone–long term catheterisation possible (up to 154 days[4,5] in situ has been recorded)
- X ray opaque throughout–aids location

1. New Eng.Jnl.Med., 265,1283, 1961 2. Arch.Surg. 110, 644, 1975. 3. Br.Jnl Clin. Eqpt., Sept. 1978
4. Lancet, 14 Oct., 1978, 825 5. Lancet, 5 Jan., 1980, 19

For details of this and other catheters in Vygon's range, complete the coupon and send it to:
Vygon (UK) Limited,
Bridge Road, Cirencester, Gloucestershire GL7 1PT
Telephone: Cirencester (0285) 67051

Please send me details of other Vygon catheters.

Name ____________________

Position ____________________

Hospital ____________________

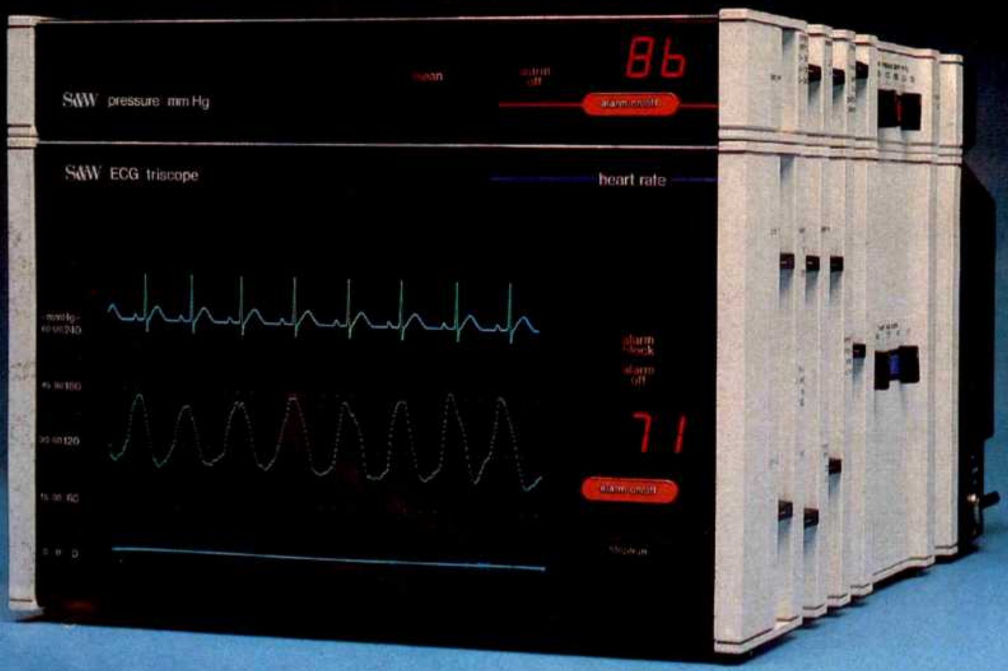
Address ____________________

____

____

VYGON

SYSTEM 8000

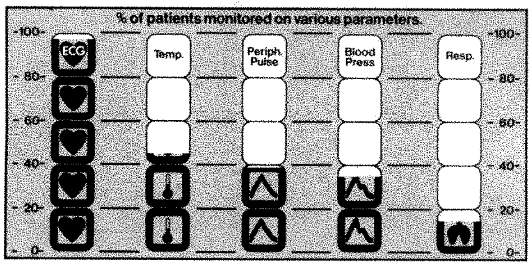


S&W

Simonsen & Weel Limited, Hatherley House, Hatherley Road, Sidcup Kent DA 14 4BR. Tel: 01-300 1128

... a different approach to Patient Monitoring

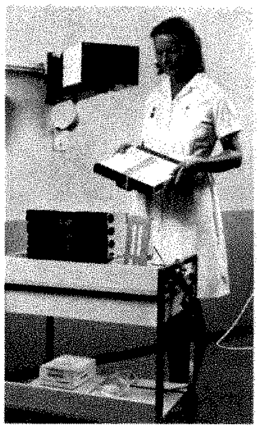
Electronic monitoring is now an accepted part of patient care. ECG is the most regularly monitored signal and the table below approximates to the percentage of patients monitored electronically for the more common parameters.



Today the cost of quality medical instrumentation does not allow there to be equipment in the Intensive or Coronary Care Unit which is not fully used or is unavailable for use on one patient because it is locked into a system on another. The S & W 8000 System allows total flexibility to match the instrumentation to the patient's need with the added advantages of:-

* Progressive expansion of the monitoring system as new modules for new parameters are developed
* Modules may be used with a low cost power supply as monitors in their own right; for example, pressure, temperature, respiration
* May be used in any department in the hospital; C.C.U., I.T.U., Operating Theatres, Neo-natal units
* Ease of servicing in event of unsatisfactory performances

The 8000 System is built to the high standards of safety and incorporates the recent advances in technology. Quality and reliability have been major design considerations. Let us show you how patient monitoring equipment should be made.



The 8000 System has been awarded the Industrial Design Award for 1979 and the Danish Plastics Industry Design prize 1979

ANESTHESIOLOGY REVIEW contributes to the continued clinical education of anesthesia practitioners.

ANESTHESIOLOGY REVIEW, published monthly, presents original articles, current information on important clinical developments, case reports, symposia, book reviews, and abstracts from the world's literature.

ANESTHESIOLOGY REVIEW helps anesthesiologists in their day-to-day practice.

Subscription, $32.50 p.a. Foreign,
$25.00 p.a. United States.
Send orders to:

ANESTHESIOLOGY REVIEW
275 Madison Avenue
New York, N.Y. 10016 U.S.A.

Anesthesiology Review
VOLUME 1
NUMBER 1
February
For Continuing Education in Clinical Anesthesiology
"And the Lord God caused a deep sleep to fall upon Adam, and he slept."

The new IVAC 630 Volumetric Infusion Pump is surely accurate and it speaks for itself

With all the safety and accuracy you'd expect from IVAC, the new IVAC 630 is without doubt the most sophisticated infusion pump ever developed.

Its unique micro-computer makes drug and fluid delivery more trouble-free than ever before. It displays a wide variety of messages, from set-up procedures to alarm situations on its easy-to-read display panel. As a result, improper set-up is unlikely and the operator knows at a glance the total volume delivered, the exact flow rate and what problems there are should an alarm situation occur.

Designed to deliver fluids in a closed system within fine tolerances, the IVAC 630 is ideal for critical infusions requiring very high or very low rates. Furthermore, the volume infused is displayed in 0.1ml increments. So, send today for details about the first infusion pump to actually speak for itself. And let us talk to you.

IVAC

IVAC
IVAC House, Bessborough Road,
Harrow, Middx. HA1 3DT.
Tel: (01) 864 9624. Telex: 8951734.

IVAC 630 Volumetric Infusion Pump

You've worked hard for your money

-now let it work hard for you.

Like you, we at Lombard rely on our hard earned skills. Our experience over many years has made us an important name in British Banking and Finance to help people like you make their money grow by depositing with us.

We have a wide range of specially designed Deposit Account Schemes offering sound rates of interest which is paid without deduction of tax at source.

For further details of our deposit facilities and current interest rates without any obligation, simply post the coupon today.

Lombard North Central
Bankers

To:
LOMBARD NORTH CENTRAL LTD,
DEPT. U942,
17 BRUTON STREET,
LONDON W1A 3DH.

Tel: 491 7050

Name:

(BLOCK CAPITALS PLEASE)

Address:

A member of the National Westminster Bank Group whose capital and reserves exceed £1,300,000,000.

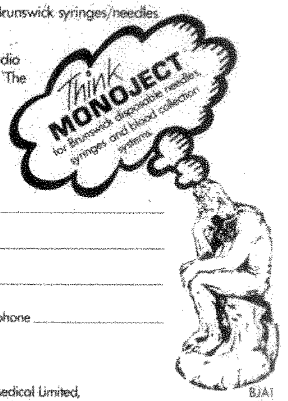
If you haven't much faith in flimsy packs, here's a firm alternative.

The Monoject range of Brunswick syringes and needles are packed in heat/sealed rigid containers to ensure perfect condition. With the heat seal unbroken, only the Brunswick range are guaranteed sterile.

☐ Please send me further details of Spinal needles for routine and specialist procedures.

☐ Please send me samples of Brunswick syringes/needles and blood collection system.

☐ Please send me details of Audio Visual Training and guide to 'The Safe Giving of Injections'.


Think MONOJECT
for Brunswick disposable needles, syringes and blood collection systems.

Name

Position

Organisation

Address

MONOJECT
DIVISION OF SHERWOOD MEDICAL
A BRUNSWICK COMPANY

Telephone

BJA1

The Monoject Division of Sherwood Medical Limited,
London Road, County Oak, Crawley, West Sussex RH10 2TL Telephone: Crawley 34501

When you require higher pressure and flows...

the MA-2 can be a lifesaver.

When extreme conditions such as status asthmaticus, aspiration pneumonitus, A.R.D.S. and Pickwickian Syndrome require ventilator therapy, you may require higher pressures and flows than are commonly available on most ventilators. Puritan-Bennett has increased the operating range of the MA-2 Volume Ventilator to provide:

- Adjustable peak system pressures up to 120 cmH_2O
- Adjustable peak flows up to 125 LPM
- Adjustable base line pressures (PEEP/CPAP) up to 45 cmH_2O

Significantly increased performance... an extra capability from Puritan-Bennett.

Puritan-Bennett International Corp.
Bognor Road, Chichester, Sussex PO19 2PH.
Telex: 86462. Cables: Puremade Chichester.
Serving Europe, the Middle East and Africa

PURITAN-BENNETT CORPORATION

10th & Harrison, Berkeley, California 94710.
Serving Japan, Australia, the Philippines, India and the Pacific Orient
7280 N.W. 58th Street, Miami, Florida 33166.
Serving Central America, South America, Mexico and the Caribbean

CANADIAN ANAESTHETISTS' SOCIETY
JOURNAL

Editor
R. A. GORDON
Assistant Editor: GORDON WYANT
Editorial Board
MARCEL BOULANGER A. W. CONN DOUGLAS B. CRAIG
KENNETH M. LEIGHTON EMERSON MOFFITT R. A. MELOCHE BERNARD PAIEMENT

The Journal is issued bi-monthly for members of the Society and Subscribers. It contains original articles and reviews on clinical and basic science subjects related to Anaesthesia.

Annual Subscription $30.00 post paid

First Class Airmail $12.00 extra (optional).

The Secretary
Canadian Anaesthetists' Society
178 St. George Street, Toronto M5R 2M7, Ontario, Canada

THE SOCIETY OF ANAESTHESIOLOGISTS OF EAST AFRICA

8TH ANNUAL SCIENTIFIC CONFERENCE

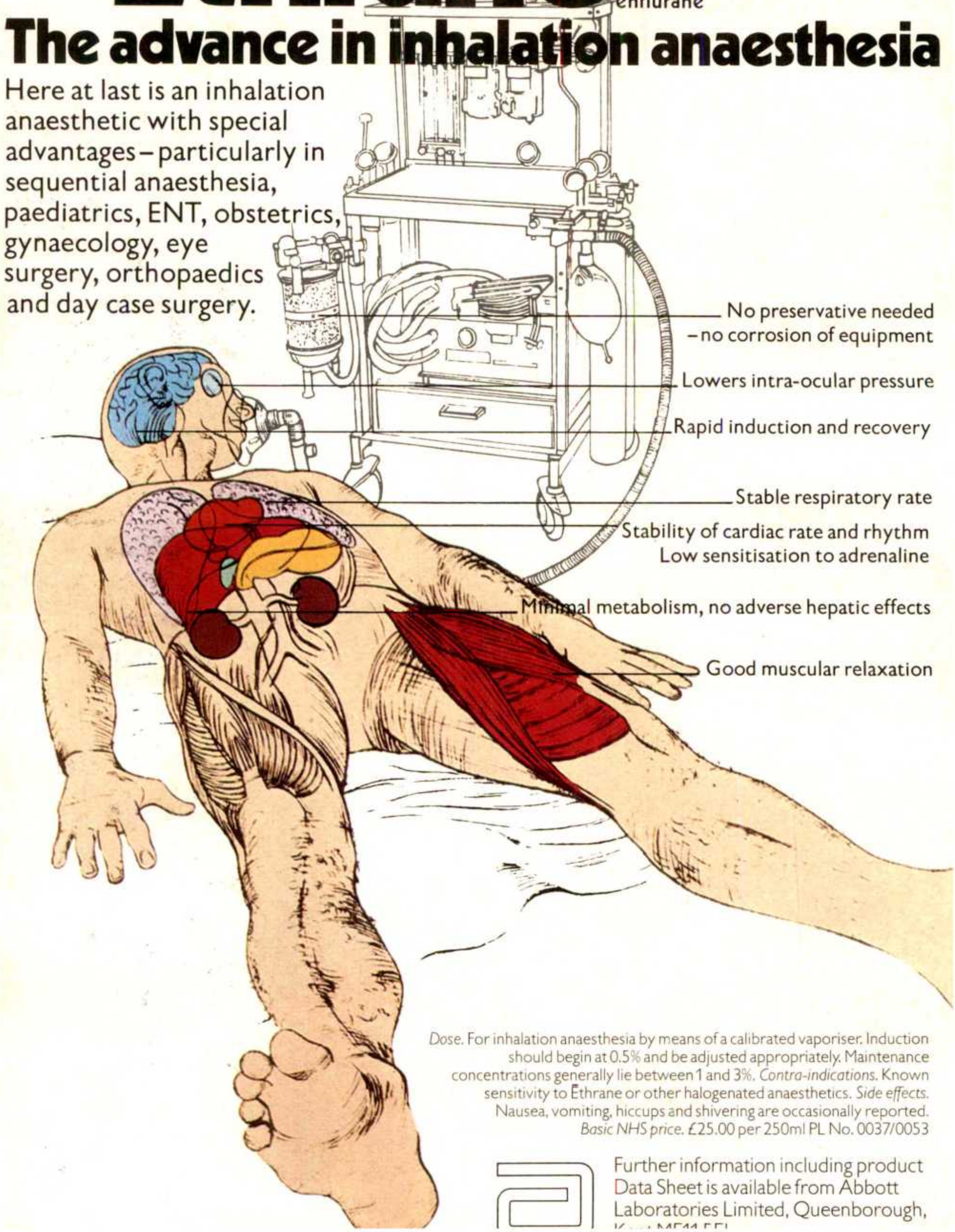
Nairobi, Kenya—October 3–5, 1980

Information is available from: Dr C. J. Omondi Nyayieka,
Hon. Secretary,
P.O. Box 20792,
Nairobi, Kenya.

Ethrane® enflurane

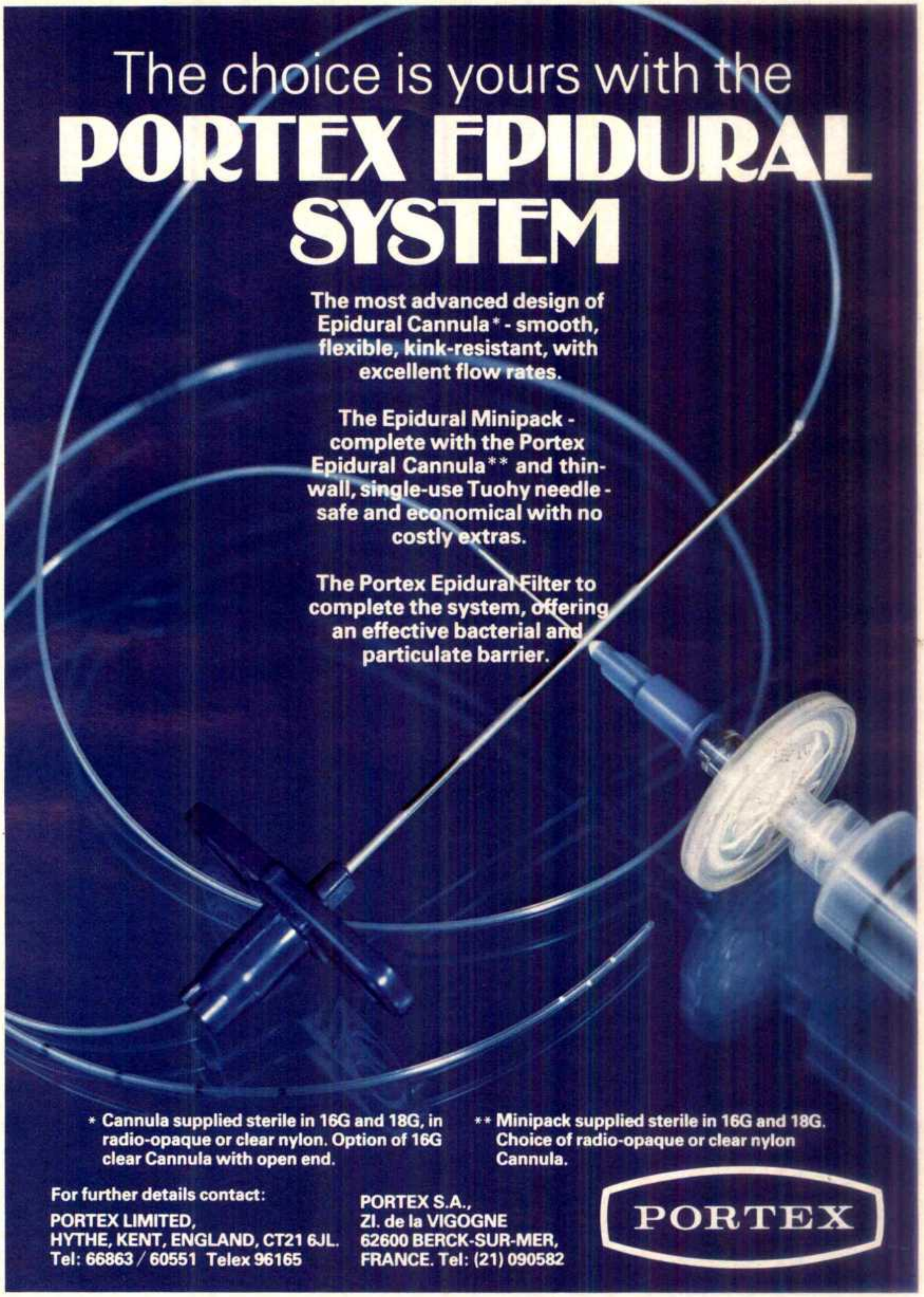
The advance in inhalation anaesthesia

Here at last is an inhalation anaesthetic with special advantages – particularly in sequential anaesthesia, paediatrics, ENT, obstetrics, gynaecology, eye surgery, orthopaedics and day case surgery.


No preservative needed – no corrosion of equipment
Lowers intra-ocular pressure
Rapid induction and recovery
Stable respiratory rate
Stability of cardiac rate and rhythm
Low sensitisation to adrenaline
Minimal metabolism, no adverse hepatic effects
Good muscular relaxation

Dose. For inhalation anaesthesia by means of a calibrated vaporiser. Induction should begin at 0.5% and be adjusted appropriately. Maintenance concentrations generally lie between 1 and 3%. *Contra-indications.* Known sensitivity to Ethrane or other halogenated anaesthetics. *Side effects.* Nausea, vomiting, hiccups and shivering are occasionally reported. *Basic NHS price.* £25.00 per 250ml PL No. 0037/0053

Further information including product Data Sheet is available from Abbott Laboratories Limited, Queenborough,



The choice is yours with the

PORTEX EPIDURAL SYSTEM

The most advanced design of Epidural Cannula* - smooth, flexible, kink-resistant, with excellent flow rates.

The Epidural Minipack - complete with the Portex Epidural Cannula and thin-wall, single-use Tuohy needle - safe and economical with no costly extras.**

The Portex Epidural Filter to complete the system, offering an effective bacterial and particulate barrier.

* Cannula supplied sterile in 16G and 18G, in radio-opaque or clear nylon. Option of 16G clear Cannula with open end.

** Minipack supplied sterile in 16G and 18G. Choice of radio-opaque or clear nylon Cannula.

For further details contact:

PORTEX LIMITED,
HYTHE, KENT, ENGLAND, CT21 6JL.
Tel: 66863 / 60551 Telex 96165

PORTEX S.A.,
ZI. de la VIGOGNE
62600 BERCK-SUR-MER,
FRANCE. Tel: (21) 090582

PORTEX

Der *Anaesthesist*

The organ of the
Austrian, German and Swiss Societies
of Anaesthesiology and Reanimation

Edited by: A. Doenicke, München; R. Frey, Mainz; O. Mayrhofer, Wein; H. Schaer, Männedorf
Managing Editor: A. Doenicke, München, Chirurgische Universitäts-Poliklivik, Anaesthesie, Pettenkoferstr. 8a, D-8000, München 2

Contents	DECEMBER 1979	
U. Ottermann, R. Dudziak, E. Appel, D. Palm	The effect of hypothermia and methoxyflurane-anaesthesia on sympatho-neuronal and sympatho-adrenal activity in the course of cardiac surgery	551
K. Huse, H. Wiecken	Circulatory changes in the sitting position during neuorsurgical anaesthesia (NLA)	557
A. Csongrady, E. Mayr, H.-D. Kamp, H.-J. Volkholz	Dosage-Problems in controlled sodium nitroprusside hypotension in oto-rhino-laryngological surgery	564
S. Fitzal, E. Knapp-Groll, W. Ilias, W. Scherzer, L. Tonczar	A comparison of two preoperative medications: responses in sedative, psychic and somatic effects	572
A. Doenicke, J. Kugler, M. Kropp, M. Laub, G. Kalbfleisch	The hypnotic effect of the new benzodiazepine derivative lormetazepam when given introvenously	578
Th. Wallenfang, U. Mielke, J. Bohl, H. Bierbach	Local myocardial necrosis and cardiac tamponade due to a central venous catheter	584

Annual subscription: DM 180 + postage

Published by SPRINGER-VERLAG · Berlin · Heidelberg · New York

---

September 14–21, 1980

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS
7th WORLD CONGRESS OF ANAESTHESIOLOGISTS
HAMBURG

Federal Republic of Germany

Deadline for submission of abstracts: January 31, 1980

Deadline for registration: May 31, 1980

Further information by:

Organizing Committee
7th World Congress of Anaesthesiologists
c/o Hamburg Messe and Congress GmbH
—Dept. for Congress Organisation—
P.O. Box 30 23 60. D-2000 Hamburg 36
Federal Republic of Germany

KRANKENHAUS ITZEHOE

Senior House Officer / Registrar

This 670-bed teaching hospital for Kiel University requires a further Senior House Officer/Registrar for the Anaesthetic and Blood Transfusion Department. The Department provides anaesthetic services for all the hospital's surgical disciplines and there is also a 12-bed intensive therapy unit.

We offer a fixed monthly salary of about 4000 DM (about £1000) for 13 months, in addition to on-duty payments of about 3000 DM monthly, a share in the head of department income from private cases and the normal employee superannuation. Moving costs will be paid.

A knowledge of German is desirable but not essential and the candidate must be a British national. The head of department is Dr J. Frick (04821/772 425).

Applications should be submitted to:

KRANKENHAUS ITZEHOE
Robert-Koch-Strasse 2
2210 Itzehoe
West Germany

Anesthesiologists:

90 member multispecialty group adjacent to modern accredited 500 bed hospital seeks Board eligible or certified specialist to join associates; located in upper midwest university metropolitan area of 110,000; thirty-five minutes from superb clean lake region; associated with four year medical school; outstanding income; all specialties represented; will pay travel expenses for physician and spouse for interview.

Write: Box 002,
c/o Macmillan Journals, Ltd,
Advertising Department,
4 Little Essex Street,
London WC2R 3LF, England

PROTECT YOUR PATIENT AND YOUR MACHINE

"Wherever possible, 'one patient use' disposables should be employed, thus eliminating most risks of cross infection and mechanical failure."[1]

The INSPIRON** Anaesthesia Breathing Circuit is designed as a single patient use product to help prevent cross contamination in hospitals.

The INSPIRON** Anaesthesia Breathing Circuit includes a Bacteria Filter of high efficiency (the filter showed no penetration in excess of 0·001%)[2] and specially designed lightweight tubes and 'Y' piece.

Nursing, November 1979. [2] As measured against U.S. Federal Standard 209b and B.S.5295 by an independent laboratory. Data available on request.
*Registered Trademark **Trademark
Rev. Date 1/80. © C. R. Bard International Limited 1980.

For further details contact:

Inspiron**

A Division of C. R. Bard International Limited,
Pennywell Industrial Estate, Sunderland, England SR4 9EW.
Tel: (0783 24) 3131 Telex: 537092.

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 4 APRIL 1980

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

EDITORIAL

STEROID ANAESTHESIA

Steroid anaesthesia has been with us for just over 40 years. The period from the accidental discovery by Hans Selye of the anaesthetic actions of some 75 naturally-occurring steroids to the present time has seen the appearance of three clinically acceptable steroid anaesthetics.

Hydroxydione (P'An et al., 1955) was a water-soluble ester of pregnanedione, the most potent of the compounds studied by Selye. It had a brief vogue as a basal anaesthetic, but its undesirable side-effects —pain on injection, prolonged onset and duration of action, and a high frequency of thrombophlebitis— —led to its gradual disappearance as a clinical anaesthetic. It was used as a continuous infusion (Robertson and Wynn-Williams, 1961). The search for further water-soluble steroids brought a disodium phosphate salt of pregnanedione (Sutton, 1972). Animal studies indicated that this had all the desired actions, but investigations in man were short-lived because the first patients complained of intense tingling in the neck and back before the onset of anaesthesia (Atkinson et al., 1965).

The introduction of Althesin, a mixture of alphaxalone and alphadolone acetate, in 1971, was unique in that the drugs were dissolved in an emulsifying agent (Cremophor EL) composed mainly of polyoxyethylated castor oil. This solution of the steroids in a micellophor could be further diluted in aqueous solutions to be administered for anaesthesia. Introduced as an induction agent, Althesin has become popular throughout most of the world, with the notable exception of the United States. One particular attribute of the drug was noted early in its development, that it is rapidly metabolized to such an extent that no cumulation was detected after repeated administration (Child et al., 1972). Although some pharmacokinetic data were available following single dose administration, the impetus to use the drug by continuous i.v. infusion for maintenance anaesthesia and to study the pharmacokinetics of the continuous infusions of Althesin in man came later (du Cailar, 1972; Savege et al., 1975; Sear and Prys-Roberts, 1979a). Studies of the fate of ^{14}C-labelled alphaxalone (Strunin et al., 1977) in man indicated that the drug was rapidly taken up from the circulation by the liver and radioactivity could be detected in the bile. In this respect it seemed that the human liver metabolized alphaxalone in the same way as the rat liver (Child et al., 1972). Recent studies using gas chromatography combined with mass spectrometry (J. W. Sear and H. L. J. Makin, unpublished observations) have failed to identify significant quantities of free alphaxalone, its metabolites or glucuronide conjugates, in bile collected from patients who received an infusion of Althesin during cholecystectomy with exploration of the common bile duct. The pattern of metabolism appears to be very different in man compared with the rat, the mechanism probably involving intrahepatic re-uptake to the blood and excretion through the kidneys.

In healthy patients the continuous infusion of Althesin at a constant rate for many hours causes a constant plasma concentration; following cessation of the infusion, the plasma concentration decreases rapidly following a two-phase exponential, and most patients waken rapidly. Some patients with liver disease clear Althesin from the circulation more rapidly than do normal subjects (Sear and Pyrs-Roberts, 1979a); this may be a result of increased hepatic blood flow resulting in an increased hepatic extraction ratio. Studies of isolated rat hepatocytes (Sear and McGivan, 1980a) suggest that the hepatic microsomal mixed function oxidase enzyme system is involved in the metabolism of the steroid anaesthetics. There is no evidence, however, that Althesin induces its own metabolism during or after long-term administration (Sear and McGivan, 1980b).

A major advantage of Althesin administered as an i.v. infusion is that the dose-dependent effects on the cardiovascular system are minimal by comparison with the volatile anaesthetic agents, although the ventilatory depressant effects are similar to those of the volatile agent (Sear and Prys-Roberts, 1979b). The marked reduction of systemic vascular resistance and the sustained cardiac output, even at fast infusion rates, may be secondary to the effects of Cremophor in reducing plasma viscosity, especially at low shear rates (Gramstad and Stovner, 1979). This may be regarded as an advantage during anaesthesia for vascular surgery, or in patients with peripheral occlusive arterial disease.

The main disadvantage of Althesin as an induction agent is the frequency of anaphylactoid responses, which can occur on either first or subsequent administration. The currently available immunological methods have not clarified the mechanisms by which any constituent of Althesin can induce an immune response. In most cases, the complement system is activated to cause anaphylaxis, but the initial trigger of either the classical or the alternate pathway of complement activation has yet to be elucidated. It is not known whether it is an effect of the drug or perhaps its vehicle (Cremophor EL) on the immune system, nor has the true frequency of the anaphylactoid response been established. There are some who, having witnessed an adverse response, have vowed never to use the drug again, and one cannot criticise such an attitude. Others, including ourselves do not regard the reported frequency of anaphylaxis (Clarke et al., 1975; Evans and Keogh, 1977) as a reason for not administering Althesin, even on more than one occasion.

Against this background, the introduction of a new water-soluble steroid anaesthetic, minaxolone, seemed most appropriate. A water-soluble compound could have major advantages if the anaphylactic responses to Althesin were caused by the vehicle rather than the drug. No other steroid compounds have been incriminated in anaphylaxis, whereas Cremophor EL is known to cause anaphylactoid responses in cats, dogs and other highly susceptible species. Early clinical studies showed minaxolone to be an acceptable agent for induction of anaesthesia (Aveling et al., 1979) and for maintenance of anaesthesia by infusion. Its main clinical disadvantage was that recovery was prolonged after short, outpatient anaesthesia compared with Althesin (Sear et al., 1980) and also after infusions of minaxolone (J. W. Sear and C. Prys-Roberts, in preparation). The prolongation of recovery is probably a consequence of the larger steady-state distribution volume of this water-soluble anaesthetic agent. During the course of the early clinical investigations minaxolone was withdrawn from use pending further long-term toxicology studies. A parallel to this situation occurred with the volatile agent isoflurane, which was also withdrawn from clinical investigation following reports that it was a carcinogenic substance (Corbett, 1976; Eger, et al., 1978), whereas, 3 years later, these reports were repudiated and isoflurane was shown to be free of carcinogenic effects.

While the further toxicological studies of minaxolone are progressing, much remains to be studied with Althesin. As a drug for continuous infusion anaesthesia, Althesin has almost all the necessary attributes, but the question of hypersensitivity responses remains. One option is to find an alternative formulation for alphaxalone in the hope of reducing the frequency of anaphylactoid responses.

Cedric Prys-Roberts
John Sear

REFERENCES

Atkinson, R. M., Davis, B., Pratt, M. A., Sharpe, H. M. and Tomich, E. G. (1965). Action of some steroids on th central nervous system. *J. Med. Chem.*, **8**, 426.

Aveling, W., Sear, J. W., Fitch, W., Chang, H., Waters, A. Cooper, G. M., Simpson, P., Savege, T. M., Prys Roberts, C., and Campbell, D. (1979). Early clinica evaluation of minaxolone, a new intravenous steroi anaesthetic agent. *Lancet*, **2**, 71.

du Cailar, J. (1972). The effects in man of infusions o Althesin with particular regard to the cardiovascula system. *Postgrad. Med. J.* (Suppl. 2), **48**, 72.

Child, K. J., Gibson, W., Harnby, G., and Hart, J. W (1972). Metabolism and excretion of Althesin (CT 1341 in the rat. *Postgrad. Med. J.* (Suppl. 2), **48**, 37.

Clarke, R. S. J., Dundee, J. W., Garrett, R. T., McArdle G. K., and Sutton, G. A. (1975). Adverse reactions t intravenous anaesthetics: a survey of 100 reports. *Br. J Anaesth.*, **47**, 575.

Corbett, T. H. (1976). Cancer and congenital anomalie associated with anaesthetics. *Ann. N.Y. Acad. Sci.*, **271** 58.

Eger, E. I., White, A. E., Brown, C. L., Biava, C. G. Corbett, T. H., and Stevens, W. C. (1978). A test of th carcinogenecity of enflurane, isoflurane, halothane methoxyflurane and nitrous oxide in mice. *Anesth Analg. (Cleve.)*, **57**, 678.

Evans, J. M., and Keogh, J. A. M. (1977). Adverse reactions to intravenous anaesthetic induction agents. *Br. Med. J.*, **2**, 735.

Gramstad, L., and Stovner, J. (1979). Plasma viscosity and Cremophor-containing anaesthetics. *Br. J. Anaesth.*, **51**, 1175.

P'An, S. Y., Gardocki, J. E., Hutcheon, D. E., Rudel, H., Kodet, M. J., and Laubach, G. D. (1955). General anesthetic and other pharmacological properties of a soluble steroid, 21-hydroxy pregnanedione sodium succinate. *J. Pharmacol. Exp. Ther.*, **115**, 432.

Robertson, J. D., and Wynn-Williams, A. (1961). Studies of the clinical and pathological effects of hydroxydione. *Anaesthesia*, **16**, 389.

Savege, T. M., Ramsay, M. A. E., Curran, J. P. J., Cotter, J., Walling, P. T., and Simpson, B. R. (1975). Intravenous anaesthesia by infusion: a technique using alphaxalone/alphadolone (Althesin). *Anaesthesia*, **30**, 759.

Sear, J. W., Cooper, G. M., Williams, N. B., Simpson, P. J., and Prys-Roberts, C. (1980). Minaxolone or Althesin supplemented by nitrous oxide: a study in anaesthesia for short operative procedures. *Anaesthesia*, **35**, (in press).

Sear, J. W., and McGivan, J. D. (1980a). The metabolism of alphaxalone by isolated rat hepatocytes. *Biochem. Pharmacol.*, **29**, 248.

—— —— (1980b). Evidence for hepatic metabolism of Althesin rate-limiting the duration of anaesthesia in the rat. *Br. J. Anaesth.*, **52**, 231P.

—— Prys-Roberts, C. (1979a). Plasma alphaxalone concentrations during continuous infusions of Althesin. *Br. J. Anaesth.*, **51**, 857.

—— —— (1979b). Dose-related haemodynamic effects of continuous infusions of Althesin in man. *Br. J. Anaesth.*, **51**, 867.

Strunin, L., Strunin, J. M., Knights, K. M., and Ward, M. E. (1977). Metabolism of ^{14}C-labelled alphaxalone in man. *Br. J. Anaesth.*, **49**, 609.

Sutton, J. A. (1972). A brief history of steroid anaesthesia before Althesin (CT 1341). *Postgrad. Med. J.* (Suppl. 2), **48**, 9.

Br. J. Anaesth. (1980), **52**, 367

ANTAGONISM OF KETAMINE–DIAZEPAM ANAESTHESIA BY 4-AMINOPYRIDINE IN HUMAN VOLUNTEERS

S. AGOSTON, P. J. SALT, W. ERDMANN, T. HILKEMEIJER, A. BENCINI AND D. LANGREHR

SUMMARY

Five healthy human volunteers were anaesthetized on two separate occasions, 1 week apart, using a standard diazepam–ketamine induction followed by an infusion of ketamine for 1 h. Ten minutes after stopping the infusion, either 4-aminopyridine 0.3 mg kg^{-1} in saline or the same volume of saline alone was administered i.v. It was concluded that 4-aminopyridine enhanced dramatically the rate of recovery of the subjects to full consciousness and normal motor co-ordination when compared with the saline controls.

The compound 4-aminopyridine (4-AP) is of interest to anaesthetists because it is a potent antagonist of the neuromuscular blocking actions of non-depolarizing myoneural blocking drugs (Lemeignan and Lechat, 1967; Paskov, Stojanov and Micov, 1973; Bowman, Harvey and Marshall, 1977; Harvey and Marshall, 1977). In fact, it has been used clinically in Bulgaria as an antagonist to tubocurarine for several years (Paskov, Stojanov and Micov, 1973; Stojanov et al., 1976).

In contrast to neostigmine, it is free from anticholinesterase activity and its mechanism of action appears to be pre-junctional (Lundh, Leander and Thesleff, 1977). It enhances the release of transmitter from the motor nerve terminals (Lundh and Thesleff, 1977; Molgo, Lemeignan and Lechat, 1977; Vizi, van Dijk and Foldes, 1977). However, this prejunctional action appears to be a general one affecting other nerve terminals also. For instance, in the periphery, 4-AP has been shown to potentiate the effects of adrenergic stimulation in the rabbit vas deferens (Johns et al., 1976) and its action here was considered to be presynaptic, resulting in an increased release of the sympathetic transmitter in response to nerve stimulation.

There is an increasing body of experimental evidence concerning the c.n.s. effects of 4-AP, suggesting that it crosses the blood–brain barrier freely. The central actions are thought to be mediated by a presynaptic mechanism similar to that seen in the periphery, and are not necessarily restricted to effects upon any particular type of synapse or transmitter. Thus, 4-AP has been shown to facilitate transmission in excitatory and inhibitory pathways in the spinal cord of the cat (Lemeignan, 1972, 1973; Jankowska et al., 1977) and the sixth ganglion of the cockroach (Hue et al., 1976). Furthermore, Nicholson and colleagues (1976) have shown that 4-AP can alter extracellular calcium and potassium concentrations in the cat cerebellum and may thereby alter the excitability of the cerebellar neurones. 4-AP has also been found to alter the turnover of monoamines in the central nervous system of rats (Andén and Leander, 1979). Finally, a central effect of 4-AP which has a direct relevance to its use in anaesthetic practice has been noted in the cat, namely, stimulation of respiratory drive as judged by phrenic nerve activity (See, Folgering and Schläfke, 1978).

Because it was observed, in experiments designed to investigate the antagonistic effect of 4-AP on tubocurarine-induced neuromuscular block in monkeys anaesthetized with high doses of ketamine, that 4-AP had a definite analeptic effect, even during an infusion of ketamine (S. Agoston, unpublished observation), we decided to look for interactions between 4-AP and ketamine. Healthy human volunteers were given a ketamine–diazepam anaesthetic and the effects of 4-AP upon the subsequent rate of recovery from this anaesthetic were monitored.

METHODS

Five healthy anaesthetists were subjected on two occasions, at least 1 week apart, to a ketamine–diazepam anaesthetic lasting 1 h. Following an injection

---

S. AGOSTON, M.D., PH.D.; P. J. SALT,* M.A., M.B., B.CHIR., PH.D.; W. ERDMANN, M.D., PH.D.,; T. HILKEMEIJER, M.D.; A. BENCINI, M.D., F.F.A.R.C.S.; D. LANGREHR, M.D., PH.D.; Research Group of Anaesthesiology and Clinical Pharmacology, Department of Anaesthesiology, University Hospital, State University of Groningen, Oosteringel 59, Groningen, The Netherlands.

* Present address: Department of Anaesthetics, Bristol Royal Infirmary, Bristol.

0007-0912/80/040367-04 $01.00

© Macmillan Journals Ltd 1980

of atropine 0.5 mg i.v., anaesthesia was induced in each subject with a bolus of diazepam 0.2 mg kg^{-1} i.v. and ketamine 2.0 mg kg^{-1} i.v. An i.v. infusion of saline containing ketamine 1 mg ml^{-1} was started. During the subsequent 60 min ketamine 1 mg kg^{-1} was infused so that each volunteer received in total ketamine 3 mg kg^{-1} during 1 h. Ten minutes after stopping the infusion of ketamine either 4-AP 0.3 mg kg^{-1} or the same volume of saline was administered i.v. Instead of measuring the "sleep time" we decided to challenge each volunteer with a battery of tests continuously after the injection of the 4-AP or the saline alone. These tests were chosen in order to obtain information about the graded return to normality of such higher cerebral functions as logical thought, recall, short- and long-term memory and general physical co-ordination. These tests are summarized in table I and consist of repeated challenging with simple mental arithmetic of increasing difficulty as the level of consciousness increased, asking the subject to read a simple sentence from a book and to recall this 15 s later, remembering dates such as his wife's birthday, the use of a calculator to perform simple arithmetic and finally the return to a fully ambulant state with no motor or sensory deficits.

TABLE I. *Time required for the successful completion of tests (min) (mean + SEM). Paired Student's t test* ($n = 5$)

Test	Saline	4-AP	P
Simple arithmetic	10.4 ± 2.1	1.7 ± 0.4	< 0.05
Handles maths problem with a calculator	29.2 ± 4.3	5.6 ± 1.2	$= 0.01$
Remembers wife's birthday	12.4 ± 1.9	3.0 ± 0.7	< 0.01
Recalls text	33.0 ± 3.7	10.8 ± 3.8	< 0.05
Return to physical normality	232 ± 20.6	30.2 ± 3.5	< 0.001

Diazepam was included in this regime in order to minimize the cardiovascular side-effects of the ketamine and allow amnesia of any undesirable hallucinatory experiences during the period of "dissociative anaesthesia" produced by the ketamine. Furthermore, the anaesthetic sequence used was similar to that utilized in clinical practice and it is hoped to extend this study to include patients receiving a comparable diazepam–ketamine anaesthetic.

RESULTS

The rate of recovery from the ketamine–diazepam anaesthesia was improved greatly on those occasions when the subjects received 4-AP, as judged by the time needed to perform the various tests (table I). Statistical analysis of the results (paired Student's *t* test) showed a significant difference in the results obtained with and without 4-AP treatment in every test used. Subjective experiences of the recovery period were the same for all volunteers. All the subjects wakened suddenly, all senses returning simultaneously, when they received 4-AP, whereas when saline was administered the subjects drifted slowly into a state of consciousness, in some cases hearing the voices of the investigators before they became aware of them visually.

The only side-effects of 4-AP noted were a tingling sensation around the lips and in one case a "vibrating feeling" along the length of the arm where the injection site was located. No ketamine-induced hallucinations were experienced with or without 4-AP.

DISCUSSION

The results show clearly that 4-AP increased the rate of recovery of the subjects from the diazepam–ketamine anaesthesia as judged by the simple tests used compared with the recovery rate when saline was injected. The dose of 4-AP used (0.3 mg kg^{-1}), was relatively small and was roughly the same as that which has been used to antagonize safely the effects of tubocurarine and pancuronium in man (Stojanov et al., 1976; Miller et al., 1979). These results may find a clinical use in the possible administration of 4-AP as a means of decreasing the sometimes prolonged recovery time of patients after a ketamine anaesthetic. This would alleviate not only the task of the recovery room nursing staff and be of benefit to the patient by returning him to a safe level of consciousness more quickly, but could perhaps be of especial use in conditions where a rapid recovery from ketamine anaesthesia is essential, as in a major disaster.

Several anaesthetic agents have been shown to alter the turnover of acetycholine in the brain of animals and the release of this putative central transmitter may be influenced by 4-AP. For instance, it is known that barbiturates inhibit the release of acetylcholine and cause its accumulation in the brain (Giarman and Pepeu, 1962; Mitchell, 1963; Celesia and Jasper, 1966; Crossland and Slater, 1968) and Rao and co-workers (1977) have demonstrated an antagonism between 4-AP and the anaesthetic effects of pentobarbitone sodium and methohexitone in the rat. Furthermore, the turnover of acetylcholine is decreased in different brain areas of the rat after halothane, enflurane or ketamine anaesthesia, each agent causing a definite pattern of changes related to the different cortical and subcortical sites of action of these agents as determined from electrophysiological studies (Ngai, Cheney and Finck, 1978). Physostigmine, the centrally-acting anticholinesterase, has been used successfully in the past to antagonize the effects of droperidol, benzodiazepines and other centrally-acting drugs used in clinical anaesthesia which are thought to act in part by interfering with central cholinergic pathways (Bidwai, Cornelius and Stanley, 1976; Hill, Stanley and Sentker, 1977). However, the indirect vagotonic action of physostigmine represents a serious disadvantage to its use, necessitating the additional administration of atropine, which itself may antagonize its c.n.s. effects (Rumack, 1973). This problem does not exist with the administration of 4-AP because of its lack of anticholinesterase activity. Indeed, Miller and colleagues (1979) have emphasized the fact that it is not necessary to give atropine when 4-AP is given in human subjects. Folgering and his co-workers have actually found evidence for antagonism of the central effects of 4-AP by atropine in the cat (See, Folgering and Schläfke, 1978; Folgering, Rutten and Agoston, 1979).

REFERENCES

Andén, N. E., and Leander, S. (1979). Effects of 4-aminopyridine on the turnover of monoamines in the central nervous system of the rat. *J. Neural Transm.*, **44**, 1.

Bidwai, A. V., Cornelius, L. R., and Stanley, T. H. (1976). Reversal of innovar-induced post-anesthetic somnolence and disorientation with physostigmine. *Anesthesiology*, **44**, 249.

Bowman, W. C., Harvey, A. L., and Marshall, I. G. (1977). The actions of aminopyridines on avian muscle. *Naunyn-Schmiedebergs Arch. Pharmacol.*, **297**, 99.

Celesia, G. G., and Jasper, H. H. (1966). Acetylcholine released from cerebral cortex in relation to state of activation. *Neurology*, **16**, 1053.

Crossland, J., and Slater, P. (1968). The effect of some drugs on the "free" and "bound" acetylcholine content of rat brain. *Br. J. Pharmacol. Chemother.*, **33**, 42.

Folgering, H., Rutten, J., and Agoston, S. (1979). Stimulation of phrenic nerve activity by an acetylcholine releasing drug: 4-aminopyridine. *Pflugers Arch.*, **379**, 181.

Giarman, J., and Pepeu, G. (1962). Drug-induced changes in brain acetylcholine. *Br. J. Pharmacol. Chemother.*, **19**, 226.

Harvey, A. L., and Marshall, I. G. (1977). The actions of three diaminopyridines on the chick biventer cervicis muscle. *Eur. J. Pharmacol.*, **44**, 303.

Hill, G. E., Stanley, T. H., and Sentker, C. R. (1977). Physostigmine reversal of postoperative somnolence. *Can. Anaesth. Soc. J.*, **24**, 707.

Hue, B., Pelhate, M., Callec, J. J., and Chanelet, J. (1976). Synaptic transmission in the sixth ganglion of the cockroach; action of 4-aminopyridine. *J. Exp. Biol.*, **65**, 517.

Jankowska, E., Lundberg, A., Rudomin, P., and Sykova, E. (1977). Effects of 4-aminopyridine on transmission in excitatory and inhibitory synapses in the spinal cord. *Brain Res.*, **136**, 387.

Johns, A., Golko, D. S., Lauzon, P. A., and Paton, D. M. (1976). The potentiating effects of 4-aminopyridine on adrenergic transmission in the rabbit vas deferens. *Eur. J. Pharmacol.*, **38**, 71.

Lemeignan, M. (1972). Analysis of the action of 4-aminopyridine on the cat lumbar spinal cord. I: Modification of the afferent volley, the monosynaptic discharge amplitude and the polysynaptic evoked responses. *Neuropharmacology*, **11**, 551.

—— (1973). Analysis of the effects of 4-aminopyridine on the lumbar spinal cord of the cat. II: Modifications of certain spinal inhibitory phenomena, post-tetanic potentiation and dorsal root potentials. *Neuropharmacology*, **12**, 641.

—— Lechat, P. (1967). Sur l'action anticurare des aminopyridines. *C. R. Acad. Sci. (Paris), Série D.*, **264**, 169.

Lundh, H., Leander, S., and Thesleff, S. (1977). Antagonism of the paralysis produced by botulinum toxin in the rat. *J. Neurol. Sci.*, **32**, 29.

—— Thesleff, S. (1977). The mode of action of 4-aminopyridine and guanidine on transmitter release from motor nerve terminals. *Eur. J. Pharmacol.*, **42**, 411.

Miller, R. D., Booij, L. H. D. J., Agoston, S., and Crul, J. F. (1979). Potentiation of neostigmine and pyridostigmine by 4-aminopyridine in man. *Anesthesiology*, **50**, 416.

Mitchell, J. F. (1963). Spontaneous and evoked release of acetylcholine from the cerebral cortex. *J. Physiol. (Lond.)*, **165**, 98.

Molgo, J., Lemeignan, M., and Lechat, P. (1977). Effects of 4-aminopyridine at the frog neuromuscular junction. *J. Pharmacol. Exp. Ther.*, **203**, 653.

Ngai, S. H., Cheney, D. L., and Finck, A. D. (1978). Acetylcholine concentrations and turnover in rat brain structures during anesthesia with halothane, enflurane and ketamine. *Anesthesiology*, **48**, 4.

Nicholson, C., Steinberg, R., Stöckle, H., and ten Bruggekate, G. T. (1976). Calcium decrease associated with aminopyridine-induced potassium increase in cat cerebellum. *Neurosci. Lett.*, **3**, 315.

Paskov, D. S., Stojanov, N. A., and Micov, V. Z. (1973). New anticurare and analeptic drug Pymadin (4-aminopyridine hydrochloride) and its use in anaesthesia (in Russian). *Eksp. Khir. Anestheziol.*, **18**, 48.

Rao, D. B. S., Nagashima, H., Deery, A. M., and Foldes, F. F. (1977). Antagonism of barbiturate anesthesia by 4-aminopyridine in the rat. *Abstracts ASA Annual Meeting*, October 1977.

Rumack, B. H. (1973). Anticholinergic poisoning: treatment with physosytigmine. *Pediatrics*, **52**, 449.

See, W. R., Folgering, M., and Schläfke, M. E. (1978). Central respiratory and cardiovascular effects of the ACh releaser: 4-aminopyridine (4-AP+). *Pflügers Arch.*, **377** (Suppl.), R20.

Stojanov, E., Vulchev, P., Shturbova, M., and Marinova, M. (1976). Clinical electromyomechanographic and electromyographic studies in the curarization with pymadine. *Anaesth. Resus. Intern. Ther.*, **4**, 139.

Vizi, E. S., van Dijk, J., and Foldes, F. F. (1977). The effect of 4-aminopyridine on acetylcholine release. *J. Neural Transm.*, **41**, 265.

ANTAGONISME DE L'ANESTHESIE A LA KETAMINE ET AU DIAZEPAM PAR LA 4-AMINOPYRIDINE SUR DES VOLONTAIRES

RESUME

Cinq volontaires en bonne santé ont été anesthésiés par deux fois, à une semaine d'intervalle. L'induction a été provoquée d'une manière standard par le diazépam et la kétamine et celle-ci a été suivie d'une infusion de kétamine pendant 1 h. Dix minutes après avoir arrêté l'infusion, on a administré par voie intraveineuse soit de la 4-aminopyridine (à raison de 0,3 mg kg^{-1}) dans du sérum physiologique, soit le même volume de sérum physiologique seul. On en a conclu que la 4-aminopyridine stimulait fortement le taux de reprise de conscience des sujets jusqu'à la pleine prise de conscience et à la coordination motrice normale, par comparaison avec les témoins n'ayant reçu que du sérum physiologique.

GEGENWIRKUNG VON 4-AMINOPYRIDIN AUF EINE KETAMIN-DIAZEPAMANÄSTHESIE BEI MENSCHLICHEN VERSUCHSPERSONEN

ZUSAMMENFASSUNG

Funf gesunde Versuchspersonen wurden bei zwei separaten Gelegenheiten, die eine Woche auseinanderlagen, durch normale Ketamin–Diazepamverabreichung narkotisiert, gefolgt von einer einstundigen Ketamininfusion. 10 min nach der Infusion wurden entweder 4-Aminopyridin 0,3 mg kg^{-1} in Salzlosung, oder dieselbe Menge Salzölsung allein intravenos verabreicht. Es ergab sich, dass die Erholungsrate der Versuchspersonen bis zum völligen Wiedererlangen des Bewusstseins und normaler motorischer Koordination durch 4-Aminopyridin ganz wesentlich erhoht wurde, wenn man den Vergleich zur Salzlosungs-Kontrollgruppe anstellte.

ANTAGONISMO DE LA ANESTESIA POR QUETAMINA-DIAZEPAM MEDIANTE AMINOPIRIDINA-4 EN VOLUNTARIOS HUMANOS

SUMARIO

Se anestesiaron a cinco voluntarios humanos sanos en dos oportunidades distintas, con intervalo de 1 semana, por medio de la inducción de quetamina–diazepam normal seguida por una infusion de quetamina durante 1 h. Diez minutos después del término de la infusión, se administró por vía i.v. ya sea 0,3 mg kg^{-1} de aminopiridina-4 en solución salina ya sea el mismo volumen de solución salina solo. Se llegó a la conclusión de que la aminopiridina-4 realzó dramáticamente la velocidad de recuperación de los sujetos en lo que se refiere al pleno conocimiento y a la coordinación motora normal cuando se comparaban con los controles que habían recibido solución salina sola.

Br. J. Anaesth. (1980), **52**, 371

EFFECT OF KETAMINE ON TRANSMISSION IN SYMPATHETIC GANGLIA

V. Mahmoodi, A. J. Byrne, T. E. J. Healy and S. Z. Hussain

SUMMARY

The effect of ketamine on sympathetic ganglion transmission has been studied using the guineapig isolated hypogastric nerve–vas deferens preparation. Ketamine produced a dose-dependent depression in the response to preganglionic stimulation (IC$_{50}$ 2.05×10^{-4} mol litre^{-1}). No change in the response to postganglionic stimulation was recorded. The anti-cholinergic activity of ketamine was confirmed using the frog isolated rectus abdominis.

An increase in arterial pressure after the injection of ketamine is well documented for various animals (McCarthy et al., 1965; Chen, Clazko and Kaump, 1967; Dowdy and Kaya, 1968; Chang, Chan and Ganendran, 1969) and in man (Domino, Chodoff and Corssen, 1965; Corssen and Domino, 1966; Morgan et al., 1971). The increase may be explained by both central or spinal effects (Traber, Wilson and Priano, 1970; Chodoff, 1972; Ivankovich et al., 1974; Slogoff and Allen, 1974; Wong and Jenkins, 1974; Millar, 1976) or peripheral actions (Virtue et al., 1967; Miletich et al., 1973; Nedergaard, 1973; Clanachan and McGrath, 1976; Hill et al., 1978). However, the relative contributions of the central and the peripheral effects of ketamine to the cardiovascular changes have not been distinguished. Interpretation has been further influenced by Johnstone (1976), who postulated a block in the reflex sympathetic nervous response to adrenergic stimuli following ketamine. This view is supported by the finding of Clanachan and McGrath (1976), who used a pithed rat preparation and demonstrated sympathetic ganglion blockade. A sustained reduction of peripheral vascular resistance after ketamine has been reported (Diaz et al., 1976). It would therefore be informative to study the effect of ketamine on transmission in sympathetic ganglia in a mammalian isolated sympathetic ganglion preparation.

METHOD

Adult male guineapigs (weight 400–500 g) were killed by a blow on the head and bled from an incision in the throat.

The vas deferens, hypogastric nerve and hypogastric plexus were dissected (Hukovic, 1961) from a freshly killed animal and suspended in a 50-ml organ bath containing Krebs solution (composition (mmol litre^{-1}): NaCl 118, KCl 4.7, CaCl$_2$ 2.5, MgSO$_4$ 1.2, NaHCO$_3$ 30, NAH$_2$PO$_4$ 1 and glucose 11.1) maintained ay 32 °C and bubbled with oxygen 95% and carbon dioxide 5%.

Conventional unshielded bipolar platinum ring electrodes were used to stimulate the hypogastric nerve (preganglionic) and a parallel platinum wire electrode was used to stimulate the postganglionic intramural nerve fibres in the vas deferens. A supramaximal rectangular wave stimulus was used; this was 50 V for the hypogastric nerve and 110–140V for transmural stimulation. Nerve and transmural stimuli were applied alternately for 20 s at 2-min intervals using a stimulus frequency of 20 Hz and a pulse width of 0.2 ms. Contraction of the vas (longitudinal shortening) was detected with an isotonic transducer (SRI) and recorded using a flat-bed pen recorder (Bryans). The responses of the preparation were allowed to stabilize for 1 h and then control recordings were made. A cumulative dose response was studied by adding dose increments of either ketamine 5×10^{-5} to 3×10^{-4} mol litre^{-1} or hexamethonium 5×10^{-6} to 8×10^{-5} mol litre^{-1} to the bath at 16-min intervals until complete blockade of the response to hypogastric nerve stimulation occurred. The effect of guanethidine 1×10^{-4} mol litre^{-1} on the response to transmural stimulation was

---

V. Mahmoodi,* M.D. (ISPH); A. J. Byrne, M.B., CH.B., F.F.A.R.C.S.; T. E. J. Healy, B.SC., M.D., F.F.A.R.C.S.; S. Z. Hussain, M.B., B.S., F.F.A.R.C.S.I.; Department of Surgery (Anaesthesia), The Medical School, Queen's Medical Centre, Nottingham.

* Present address: Department of Anaesthesia, University of Shiraz, Iran.

Correspondence to Dr Healy.

0007–0912/80/040371–05 $01.00

© Macmillan Journals Ltd 1980

then recorded. The preparation was washed thoroughly with Krebs solution and the recovery in the response to preganglionic and postganglionic stimulation was recorded. The effect of each drug was measured in five separate guineapig preparations.

Frogs (*Rana temporaria*) were killed by a blow on the head and then pithed. The rectus abdominis muscles were dissected and divided. Each part was suspended in a 20-ml organ bath containing frog Ringer solution at 18 °C (composition (mmol litre^{-1}): NaCl 112, KCl 2.0, $CaCl_2$ 1.8, $NaHCO_3$ 2.4) and bubbled with air. Contraction of the muscle was detected using an isotonic transducer (SRI) and recorded using a flat-bed recorder (Bryans). At the start of each experiment the recording system was calibrated by stepwise linear displacement of the transducer arm over the range produced by tissue contraction. There was a linear relation between displacement and pen excursion. All contractions are expressed in units of pen excursion (arbitrary units) and the same apparatus was used for all the experiments. Two series of experiments were performed:

(a) The response of the muscle to the addition to the Ringer solution of carbachol 20 µg (5.45×10^{-6} mol litre^{-1}) or KCl 50 mg (3.34×10^{-2} mol litre^{-1}) was recorded. A log dose–response curve to ketamine 1×10^{-5} to 4×10^{-4} mol litre^{-1} was then obtained in the presence of carbachol 5.46×10^{-6} mol litre^{-1} and in the presence of KCl 3.34×10^{-2} mol litre^{-1}.

(b) Log dose–response curves were obtained for the addition of carbachol 2, 5, 10, 20, 40 and 60 µg to the Ringer solution in the bath, which gave a concentration range of carbachol 5.46×10^{-7} to 1.6×10^{-5} mol litre^{-1}. The experiment was repeated in the presence of ketamine 1×10^{-4} mol litre^{-1}.

Ketamine was allowed a contact time of 20 min before carbachol was added to the bath. Contraction responses were measured after a carbachol contact time of 5 min and at the completion of the response to potassium chloride. The muscle was thoroughly washed and allowed to rest for 5 min after each response to carbachol or potassium chloride. Each study was made using six separate preparations.

RESULTS

Isolated sympathetic ganglia

Ketamine produced a dose-dependent reduction in the response to preganglionic stimulation. The effect of each concentration of ketamine is expressed as the percentage change in response from the control response (table I). For comparison, the effect of a classical ganglion blocking agent, hexamethonium, on the response to preganglionic stimulation is shown in table I. Both agents reduced the response to hypogastric nerve stimulation (preganglionic) but did not reduce the response to transmural stimulation (postganglionic). The response to postganglionic stimulation was blocked by guanethidine 1×10^{-4} mol litre^{-1}.

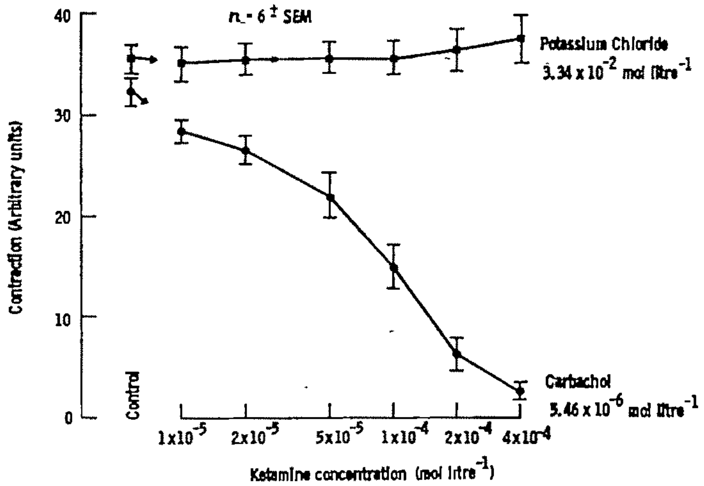


FIG. 1. Effect of ketamine on the contraction response of the frog rectus abdominis muscle to carbachol 5.46×10^{-6} mol litre^{-1} or potassium chloride 3.34×10^{-2} mol litre^{-1}.

TABLE I. *Mean percentage change in response of the vas deferens to preganglionic nerve stimulation* ($\pm$ *SEM*) (*five observations*) *in presence of ketamine or hexamethonium*

Ketamine (mol litre^{-1})	5×10^{-5}	1×10^{-4}	1.5×10^{-4}	2×10^{-4}	2.5×10^{-4}	3×10^{-4}
Per cent change in response	0	4.0 ± 1.58	8.2 ± 2.65	37.8 ± 7.75	76.0 ± 6.87	97.2 ± 2.8
Hexamethonium (mol litre^{-1})	5×10^{-6}	1×10^{-5}	2×10^{-5}	4×10^{-5}	8×10^{-5}	
Per cent change in response	5.6 ± 2.94	11.0 ± 3.46	19.0 ± 3.63	81.4 ± 7.43	100	

TABLE II. *Mean concentrations for 50% reduction of the response of the vas deferens to preganglionic stimulation* (IC_{50}). *These values were calculated from regression lines fitted to log concentration–effect curves* (*correlation coefficients are shown*)

	IC_{50} (mol litre^{-1})	Correlation coefficient
Hexamethonium	2.5×10^{-5}	$r = 0.87$ ($P<0.01$)
Ketamine	2.05×10^{-4}	$r = 0.9$ ($P<0.01$)

At large concentrations ketamine produced complete blockade of ganglionic transmission. Regression lines were calculated for the linear range of the log concentration–response curves and these were used to calculate for each drug the concentration which would produce a 50% inhibition of the response to preganglionic stimulation (IC_{50}) (table II). In the concentrations used, ketamine did not alter pH of the Krebs solution.

Rectus abdominis

The addition of carbachol to the organ bath produced a dose-related increase in the contraction response of the preparation. The contraction response to carbachol 5.46×10^{-6} mol litre^{-1} was approximately 75% of the maximum response, and ketamine produced a concentration-dependent reduction in the muscle contraction to this concentration of carbachol (fig. 1). The regression line was calculated and used to calculate the concentration of ketamine which would produce a 50% inhibition of the response to carbachol 5.46×10^{-6} mol litre^{-1}. This was ketamine 8.5×10^{-5} mol litre^{-1} ($r = 0.83$, $P<0.001$). The response of the preparation to the non-specific muscle stimulant potassium chloride 3.34×10^{-2} mol litre^{-1} was unchanged by the concentrations of ketamine used in this study.

Ketamine 1×10^{-4} mol litre^{-1} caused a reversible depression in the response of the preparation to all concentrations of carbachol tested (fig. 2). Regression lines were calculated and the slopes of the response curves were shown by analysis of covariance to be significantly different ($P<0.005$).

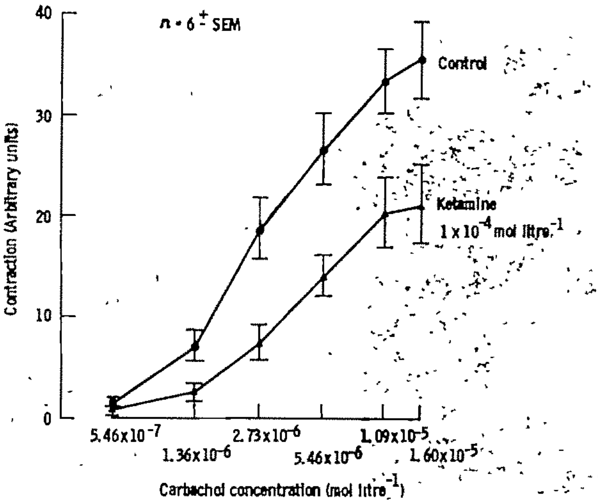


FIG. 2. Dose-response curves to carbachol using the frog rectus abdominis muscle: control and in the presence of ketamine 1×10^{-4} mol litre^{-1}.

DISCUSSION

The cardiovascular changes observed after the injection of ketamine are well recognized, but there is no widespread agreement concerning the relative contributions of the separate mechanisms to these changes. Tachycardia, increased cardiac output and increase in arterial pressure have been shown to result from a central action (Traber, Wilson and Priano, 1970; Chodoff, 1972; Ivankovich et al., 1974; Slogoff and Allen, 1974; Wong and Jenkins, 1974; Millar, 1976) and peripheral actions (Virtue et al., 1967; Miletich et al., 1973; Nedergaard, 1973; Clanachan and McGrath, 1976; Hill et al., 1978). It can only be assumed that, with variations in the conditions of the investigation, the effect at a particular site of action may assume greater importance. However, it is valuable to identify all the potential sites of action so that interaction between ketamine and other drugs acting simultaneously may be avoided or controlled.

There is evidence that ketamine potentiates the action of tubocurarine at the neuromuscular junction (Cronelly et al., 1973; Johnston, Miller and Way, 1974). We might expect, therefore, a similar reduction in nerve impulse transmission through sympathetic ganglia. However, if there is a reserve of conduction capacity in sympathetic ganglia this may disguise the effect of partial sympathetic blockade produced by the concentrations of ketamine achieved in clinical practice. Furthermore, ketamine has been shown to potentiate the response of rat isolated atria to noradrenaline (Byrne, Tomlinson and Healy, 1979) and to inhibit neuronal uptake of noradrenaline (Byrne, Healy and Tomlinson, 1979) and therefore the cardiovascular effects of central stimulation by ketamine may be maintained in spite of partial ganglion blockade. However, the simultaneous use of ketamine and other drugs which further reduce transmission in sympathetic ganglia may lead to marked haemodynamic changes. It was therefore important to examine the action of ketamine on the ganglion synapse by using an *in vitro* isolated preparation.

An isolated preparation avoids the interaction of other factors which include the integration of residual nerve cell impulse discharge and the activity of intermedio-lateral cells in the spinal cord which may reduce the sensitivity of the results obtained in the pithed rat preparation used by Clanachan and McGrath (1976).

In the present study we have shown a marked reduction in the response to preganglionic stimulation in a ketamine dose range which does not alter the response to postganglionic stimulation. We have confirmed the findings of Kraunak, Pleuvry and Rees (1977), that ketamine has an anticholinergic effect. However, the results do not allow us to characterize the blockade in detail, other than to suggest that simple competition between ketamine and cholinergic agents is unlikely.

Ketamine is often used to induce anaesthesia in patients who are compensating for a reduced blood volume by vasoconstriction and tachycardia. It would seem prudent to avoid the use of agents which, by interfering with ganglionic transmission, may augment the ganglion blocking action of ketamine and reduce the protective compensation.

ACKNOWLEDGEMENT

We would like to thank Parke-Davis for their very generous financial support.

REFERENCES

Byrne, A. J., Healy, T. E. J., and Tomlinson, D. R. (1979). The effects of ketamine on noradrenergic transmission and the response to noradrenaline in rat smooth muscle. *Br. J. Pharmacol*, **67**, 462P.

—— Tomlinson, D. R., and Healy, T. E. J. (1979). Effect of ketamine on autonomic transmission in rat isolated atria. *Br. J. Anaesth.*, **51**, 989P.

Chang, P., Chan, K. E., and Ganendran, A. (1969). Cardiovascular effects of 2-(o-chlorophenyl)-2-methylaminocyclohexanone (CL-581) in rats. *Br. J. Anaesth.*, **41**, 391.

Chen, G., Clazko, A. G., and Kaump, D. H. (1967). Revised laboratory summary. Clinical Research Information. Michigan, U.S.A.: Parke-Davis and Co.

Chodoff, P. (1972). Evidence for central adrenergic action of ketamine: report of a case. *Anesth. Analg.* (*Cleve.*), **51**, 247.

Clanachan, A. S., and McGrath, J. C. (1976). Effects of ketamine on the peripheral autonomic nervous system of the rat. *Br. J. Pharmacol.*, **58**, 247.

Corssen, G., and Domino, E. F. (1966). Dissociative anaesthesia. Further pharmacologic studies and first clinical experience with the phencyclidine derivative CL-581. *Anesth. Analg.* (*Cleve.*), **45**, 29.

Cronelly, R., Dretchen, K. L., Sokoll, M. D., and Long, J. P. (1973). Ketamine: myoneural activity and interactions with neuromuscular blocking drugs. *Eur. J. Pharmacol.*, **22**, 17.

Diaz, F. A., Bianco, J. A., Bello, A., Beer, N., Velarde, H., Izquierdo, J. P., and Jaen, R. (1976). Effects of ketamine on canine cardiovascular function. *Br. J. Anaesth.*, **48**, 941.

Domino, E. F., Chodoff, P., and Corssen, G. (1965). Pharmacological effects of CL-581, a new dissociative anaesthetic in man. *Clin. Pharmacol. Ther.*, **6**, 279.

Dowdy, E. G., and Kaya, K. (1968). Studies of the mechanism of cardiovascular responses to CL-581. *Anesthesiology*, **29**, 931.

Hill, G. E., Wong, K. E., Shaw, L., Sentker, C. R., and Blatnick, R. A. (1978). Interactions of ketamine with vasoactive amines at normothermia and hypothermia in the isolated rabbit heart. *Anesthesiology*, **48**, 315.

Hukovic, S. (1961). Responses of the isolated sympathetic nerve-ductus deferens preparation of the guineapig. *Br. J. Pharmacol.*, **16**, 188.

Ivankovich, A. D., Miletich, D. J., Reimann, C., Albrecht, R. F., and Zahed, B. (1974). Cardiovascular effects of centrally administered ketamine in goats. *Anesth. Analg.* (*Cleve.*), **53**, 924.

Johnston, R. R., Miller, R. D., and Way, W. L. (1974). The interaction of ketamine with d-tubocurarine, pancuronium and succinylcholine in man. *Anesth. Analg.* (*Cleve.*), **53**, 496.

Johnstone, M. (1976). The cardiovascular effects of ketamine in man. *Anaesthesia*, **31**, 873.

Kraunak, P., Pleuvry, B. J., and Rees, J. M. H. (1977). *In vitro* study of interactions between anaesthetics and neuromuscular blocking agents. *Br. J. Anaesth.*, **49**, 765.

McCarthy, D. A., Chen, G., Kaump, D. H., and Ensor, C. (1965). General anaesthetic and other pharmacological properties of 2 (o-chlorophenyl)-2-methylamino cyclohexane (CL-581). *J. New Drugs*, **5**, 21.

Miletich, D. J., Ivankovich, A. D., Albrecht, R. F., Zahed, B., and Ilahi, A. A. (1973). The effect of ketamine on catecholamine metabolism in the isolated perfused rat heart. *Anesthesiology*, **39**, 271.

Millar, R. A. (1976). On the mechanism and occurrence of cardiovascular stimulation by ketamine. *Br. J. Anaesth.*, **268**, 48.

Morgan, M. L., Lon, L., Singer, L., and Moore, P. H. (1971). Ketamine as the sole anaesthetic agent for minor surgical proceedings. *Anaesthesia*, **26**, 158.

Nedergaard, O. A. (1973). Cocaine-like effect of ketamine on vascular adrenergic neurones. *Eur. J. Pharmacol.*, **23**, 153.

Slogoff, S., and Allen, G. W. (1974). The role of baroreceptors in the cardiovascular response to ketamine. *Anesth. Analg.* (*Cleve.*), **53**, 704.

Traber, D. L., Wilson, R. B., and Priano, L. L. (1970). Blockade of the hypertensive response to ketamine. *Anesth. Analg.* (*Cleve.*), **49**, 420.

Virtue, R. W., Alanis, J. M., Mori, M., Lafargue, R. T., Vogel, J. H. K., and Metcalf, D. R. (1967). An anesthetic agent 2-orthochlorophenyl, 2-methylamino cyclohexanone-HCl (CL-581). *Anesthesiology*, **28**, 823.

Wong, D. H. W., and Jenkins, C. C. (1974). An experimental study of the mechanism of action of ketamine on the central nervous system. *Can. Anaesth. Soc. J.*, **21**, 57.

EFFETS DE LA KETAMINE SUR LA TRANSMISSION DES GANGLIONS SYMPATHIQUES

RESUME

On a étudié les effets de la kétamine sur la transmission du ganglion sympathique en utilisant une préparation de nerve hypogastrique–vas deferens isolés du cochon d'inde. La kétamine a produit une dépression dont l'importance a été fonction de la dose dans sa réaction à la stimulation préganglionaire (IC_{50} $2{,}05 \times 10^{-4}$ mol litre^{-1}). On n'a enregistré aucune variation dans la réaction à la stimulation postganglionnaire. L'activité anticholinergique de la kétamine a été confirmée par l'utilisation du grand droit abdominal isolé du crapaud.

WIRKUNG VON KETAMIN AUF SYMPATHISCHE GANGLIENÜBERTRAGUNG

ZUSAMMENFASSUNG

Die Wirkung von Ketamin auf die Übertragung in den sympathischen Ganglien wurde anhand eines Präparates des hypogastrischen Nerven und des Ductus deferens eines Meerschweinchens studiert. Ketamin bewirkte eine dosisabhängige Depression der Reaktion auf prägangglionische Stimulierung (IC_{50} $2{,}05 \times 10^{-4}$ mol litre^{-1}). Keine Reaktionsänderung auf postganglionische Stimulierung wurde festgestellt. Die anticholinergische Aktivität von Ketamin wurde anhand eines isolierten Präparates des Rectus abdominis eines Frosches bestätigt.

EFECTO DE LA QUETAMINA SOBRE LA TRANSMISION DE LOS GANGLIOS SIMPATICOS

SUMARIO

Se llevó a cabo el estudio del efecto de la quetamina sobre la transmisión de los ganglios simpáticos, al usar una preparación vas deferens-nervio hipogástrico aislado del cochino de la India. La quetamina produjo una depresión dependiente de la dosis en la respuesta a la estimulación pregangliónica (IC_{50} $2{,}05 \times 10^{-4}$ mol litre^{-1}). No hubo cambio alguno en la respuesta a la estimulación postgangliónica. Se confirmó la actividad anti-colinérgica de la quetamina al usar el rectus abdominis aislado de una rana.

Br. J. Anaesth. (1980), **52**, 377

SITE OF THE MUSCLE CELL ABNORMALITY IN SWINE SUSCEPTIBLE TO MALIGNANT HYPERPYREXIA

F. OKUMURA, B. D. CROCKER AND M. A. DENBOROUGH

SUMMARY

In vitro studies, using agents which act specifically on different parts of the muscle contractile mechanism, suggest that the abnormality in malignant hyperpyrexia susceptible (MHS) swine muscle lies distal to the postjunctional membrane, and that it is not a result of widespread acetylcholine receptors throughout the muscle membrane. Two possible sites are involved, one being the sarcolemma and the T-system, the other the excitation–contraction coupling mechanism and the sarcoplasmic reticulum.

When muscle from individuals or swine susceptible to malignant hyperpyrexia (MHS) is exposed to anaesthetic agents such as halothane or suxamethonium, an excess of calcium ions develops in the myoplasm, and muscle contraction occurs. The reason for this is unknown.

In the present investigation, agents which act specifically on different parts of the muscle contractile mechanism have been used in an attempt to define the site of the abnormality in MHS swine muscle. The effects of acetylcholine, tubocurarine, glycerol treatment, dantrolene sodium and deuterium oxide (D_2O) on MHS swine muscle have been examined.

The effect of acetylcholine on MHS muscle was studied since chronically denervated muscle shows an increased sensitivity to acetylcholine (Rosenblueth and Luco, 1937), and because of the suggestion that MHS muscle may be denervated (Moulds, 1978). Tubocurarine combines with the cholinoceptive site at the postjunctional membrane and blocks the transmitter action of acetylcholine (Koelle, 1975). Glycerol treatment of muscle fibres was developed by Fujino, Yamaguchi and Suzuki (1961), and has been shown by electron microscopy to disrupt the T-system (Eisenberg and Eisenberg, 1968). Dantrolene sodium, at concentrations less than 10 μmol litre^{-1}, inhibits the site where the signal is transmitted from the T-system to the sarcoplasmic reticulum (SR) without affecting the membrane potential or neuromuscular transmission (Ellis and Carpenter, 1972; Putney and Bianchi, 1974). Deuterium oxide depresses muscle contraction by inhibiting the processes by which depolarization of the T-system is transmitted to SR (Kaminer, 1960) without affecting the contractility of the myofibrils.

MATERIALS AND METHODS

Muscle biopsies were taken from the gracilis muscle in eight MHS swine.

The anaesthetic methods (Okumura, Crocker and Denborough, 1979) and the methods of preparing the muscle strips for pharmacological testing and for measurements (Moulds and Denborough, 1974) have been described previously.

The stock solutions of the drugs used to induce muscle contraction were caffeine 100 mmol litre^{-1} in muscle buffer, KCl 4 mmol litre^{-1} in water, suxamethonium chloride 5% in water, thymol 50 mmol litre^{-1} in ethanol and acetylcholine chloride 25 mmol litre^{-1} in water. Halothane was administered by passing carbogen through a calibrated Dragewick vaporizer. Tubocurarine 1.47 mmol litre^{-1} in water and dantrolene sodium 150 μmol litre^{-1} in sodium hydroxide 100 mmol litre^{-1} were used as neuromuscular blocking agents.

Glycerinated muscle fibres were prepared by immersing the fibres for 1 h at 37 °C in muscle buffer to which glycerol 400 mmol litre^{-1} had been added and through which carbogen was bubbled continuously (Howell and Jenden, 1967).

D_2O-muscle buffer was prepared by dissolving the buffer salts in D_2O instead of water. The composition of the buffer (mmol litre^{-1}) was NaCl 121.2, KCl

---

F. OKUMURA,* M.D., PH.D.; B. D. CROCKER, B.SC.; M. A. DENBOROUGH, M.D., D.PHIL., D.SC., F.R.C.P., F.R.A.C.P.; Department of Clinical Science, John Curtin School of Medical Research, The Australian National University, Canberra, A.C.T. 2601, Australia.

* Present address: Department of Anesthesiology, National Cardiovascular Centre, Osaka, Japan 565.

0007–0912/80/040377–07 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *The effects of pretreatment with tubocurarine and dantrolene sodium on contractures of malignant hyperpyrexia susceptible muscle induced by caffeine* 2 *mmol litre*$^{-1}$, *halothane* 3%, *suxamethonium* 1 *mmol litre*$^{-1}$, *KCl* 80 *mmol litre*$^{-1}$ *and thymol* 100 *mmol litre*$^{-1}$. (*Mean* ± *SEM*)

Drugs	No. of muscle preparations	Muscle contracture (g)	*P* value
Caffeine 2 mmol litre^{-1}	47	0.549 ± 0.089	—
Tubocurarine 0.06 mmol litre^{-1} + caffeine 2 mmol litre^{-1}	6	0.418 ± 0.095	0.61 (n.s.)
Dantrolene sodium 3 µmol litre^{-1} + caffeine 2 mmol litre^{-1}	6	0.087 ± 0.034	0.07 (n.s.)
Halothane 3%	58	0.635 ± 0.091	—
Tubocurarine 0.06 mmol litre^{-1} + halothane 3%	4	0.955 ± 0.247	0.38 (n.s.)
Dantrolene sodium 3 µmol litre^{-1} + halothane 3%	8	0.067 ± 0.022	0.02
Suxamethonium 1 mmol litre^{-1}	46	0.337 ± 0.042	—
Tubocurarine 0.06 mmol litre^{-1} + suxamethonium 1 mmol litre^{-1}	5	0.188 ± 0.058	0.26 (n.s.)
Dantrolene sodium 3 µmol litre^{-1} + suxamethonium 1 mmol iitre^{-1}	9	0.033 ± 0.021	0.003
Thymol 100 µmol litre^{-1}	30	0.757 ± 0.138	—
Tubocurarine 0.06 mmol litre^{-1} + thymol 100 µmol litre^{-1}	3	0.797 ± 0.118	0.93 (n.s.)
Dantrolene sodium 3 µmol litre^{-1} + thymol 100 µmol litre^{-1}	4	0.043 ± 0.025	0.07 (n.s.)
KCl 80 mmol litre^{-1}	34	1.211 ± 0.215	—
Tubocurarine 0.06 mmol litre^{-1} + KCl 80 mmol litre^{-1}	6	1.637 ± 0.445	0.46 (n.s.)
Dantrolene sodium 3 µmol litre^{-1} + KCl 80 mmol litre^{-1}	5	0.166 ± 0.082	0.08 (n.s.)

5.4, $MgSO_4$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 15.0, $CaCl_2$ 2.5 and glucose 11.5.

In the experiments involving glycerol treatment or D_2O buffer, a 30-V twitch stimulation was given to the muscle preparation by a stimulator (Model S4E, Grass Instrument Company). Glycerol and D_2O abolished the twitch response.

Statistical methods

Muscle for the tubocurarine or dantrolene pretreatment experiments came from six MHS swine, any particular test having been conducted on one to four muscle preparations from an individual pig. As these numbers were too small to assess within-pig variability for variance analysis of the data, the variances presented in table I for the pretreatment experiments using dantrolene or tubocurarine express between-pig variability.

The statistical analysis of data on the contracture of MHS swine muscle using caffeine 2 mmol litre^{-1}, halothane 3%, suxamethonium 1 mmol litre^{-1}, thymol 100 µmol litre^{-1} and KCl 80 mmol litre^{-1} was summarized in an earlier paper (Okumura, Crocker and Denborough, 1979).

P values were obtained using Student's *t* test for equal population variances.

RESULTS

Acetylcholine in concentrations of 10–100 µmol litre^{-1} did not induce contractures in MHS swine muscle preparations (fig. 1).

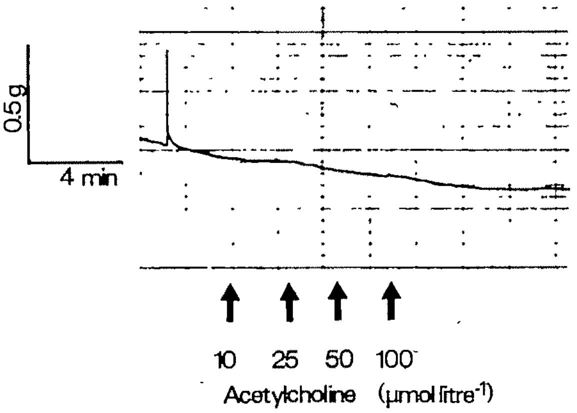


FIG. 1. Failure of acetylcholine to induce contracture of MHS swine muscle *in vitro.*

Tubocurarine did not prevent or reverse muscle contractures induced by caffeine 2 mmol litre^{-1}, halothane 3%, suxamethonium 1 mmol litre^{-1} or thymol 100 µmol litre^{-1}, and did not inhibit contractures following KCl 80 mmol litre^{-1} (fig. 2, table I).

Potassium chloride 80 mmol litre^{-1} and suxamethonium 1 mmol litre^{-1} contractures did not occur in glycerinated muscle fibres. Caffeine 2 mmol litre^{-1}, halothane 3% and thymol 100 µmol litre^{-1} contractures were considerably diminished in glycerinated muscle fibres, but higher concentrations of caffeine and thymol produced contractures (fig. 3).

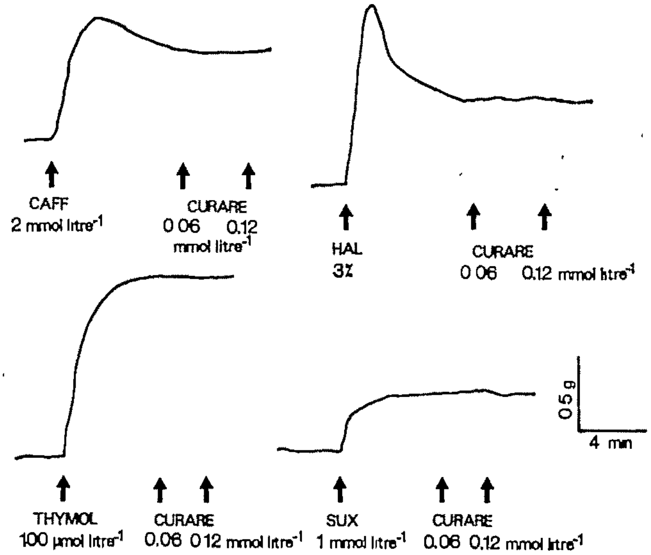


FIG. 2. Failure of tubocurarine (CURARE) to reverse contractures induced by caffeine (CAFF), halothane (HAL), thymol and suxamethonium (SUX) in MHS swine muscle *in vitro*.

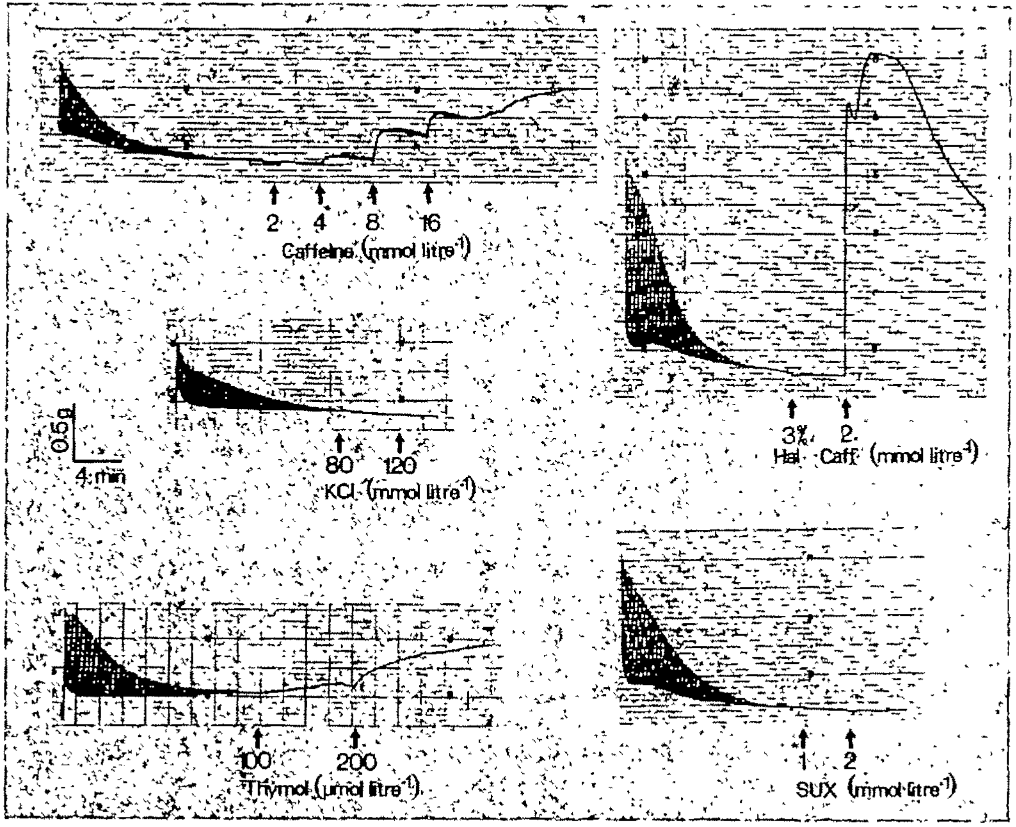


FIG. 3. The effect of glycerinating muscle fibres on caffeine, thymol, halothane, suxamethonium (SUX) and KCl contractures in MHS swine muscle *in vitro*. Note that the halothane potentiated caffeine contracture is preserved. A 30-V twitch stimulation was given to the muscle at the start of the experiments.

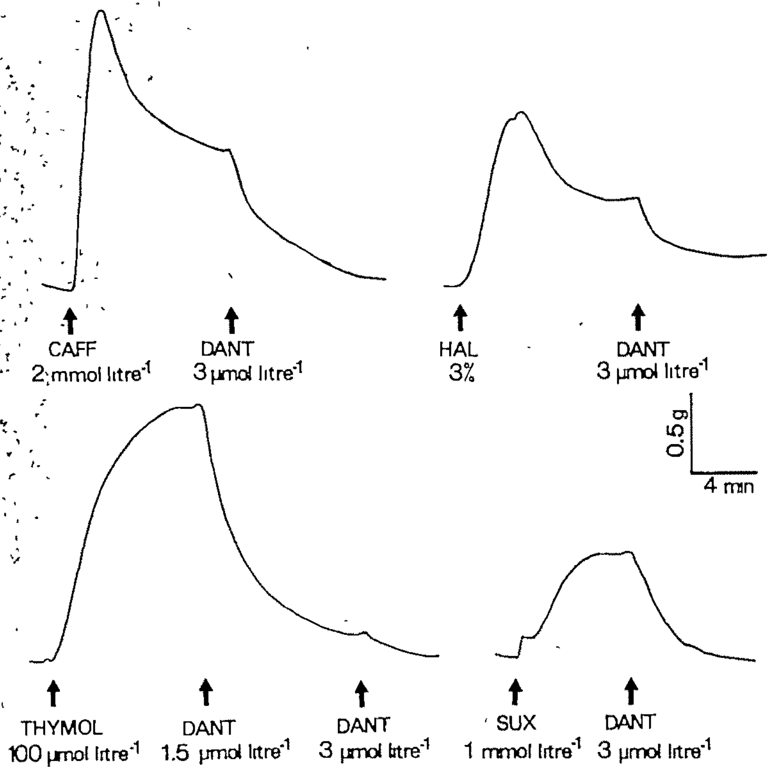


FIG. 4. The effect of dantrolene sodium on caffeine, halothane, thymol and suxamethonium (SUX) induced contractures in MHS swine muscle *in vitro*.

Dantrolene sodium 3 µmol litre^{-1} reversed contractures caused by caffeine 2 mmol litre^{-1}, halothane 3%, suxamethonium chloride 1 mmol litre^{-1} and thymol 100 µmol litre^{-1} (fig. 4). The same dose of dantrolene sodium significantly inhibited contractures induced by halothane 3% and suxamethonium 1 mmol litre^{-1}. The inhibitory effect of dantrolene sodium on caffeine, thymol and KCl contractures was not statistically significant (table I).

D_2O pretreatment completely inhibited contractures by any of the five drugs (fig. 5).

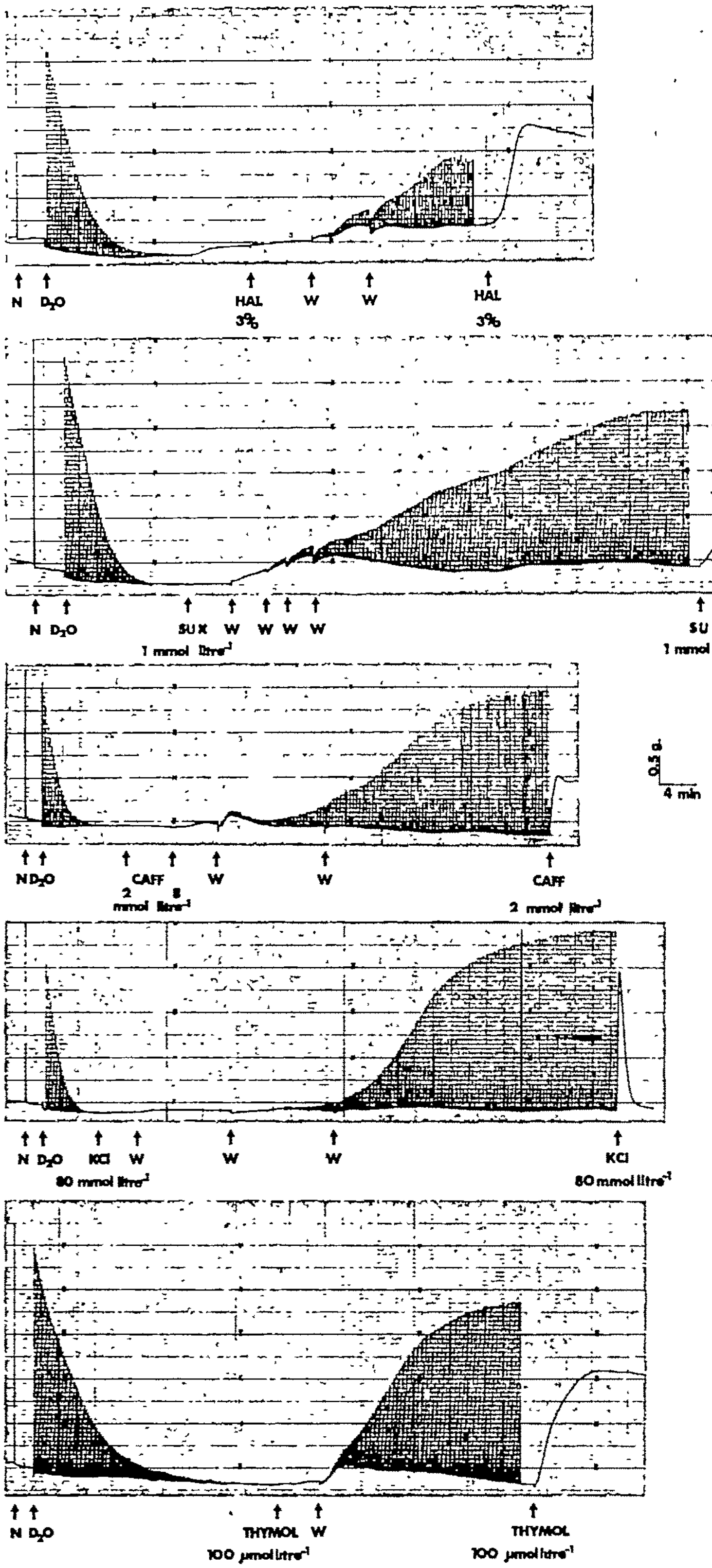
DISCUSSION

MHS muscle contracts more than normal muscle in response to halothane, suxamethonium, caffeine and KCl both in humans (Moulds and Denborough, 1974) and in swine (Okumura, Crocker and Denborough, 1979).

Suxamethonium and acetylcholine act by depolarizing the postjunctional membrane, but because suxamethonium is metabolized at a slower rate than acetylcholine its action is prolonged. Chronically denervated muscle shows an increased sensitivity to acetylcholine (Rosenblueth and Luco, 1937), to suxamethonium (Thesleff, 1974) and to caffeine (Gutman and Sandow, 1965). One explanation for this increase in sensitivity might be that acetylcholine receptors develop not only at the end-plate, but throughout the muscle membrane (Axelsson and Thesleff, 1959; Miledi, 1960). In the present investigation acetylcholine did not induce contracture in MHS muscle, and tubocurarine, in a concentration great enough to block the transmitter action of acetylcholine (Auerbach and Betz, 1971), did not affect the contracture produced by suxamethonium in MHS swine muscle. This suggests that the

---

FIG. 5. The effect of D_2O on halothane, suxamethonium (SUX), caffeine, KCl and thymol contractures induced in MHS swine muscle *in vitro*. A 30-V twitch stimulus was given to the muscle preparations at the start of the experiments. N = normal muscle buffer, W = wash with normal muscle buffer.


N
D2O
HAL 3%
W
W
HAL 3%
N
D2O
SUX 1 mmol litre-1
W
W
W
W
SUX 1 mmol litre-1
N D2O
CAFF 2 8 mmol litre-1
W
W
CAFF 2 mmol litre-1
0.5 g
4 min
N
D2O
KCl 80 mmol litre-1
W
W
W
KCl 80 mmol litre-1
N
D2O
THYMOL 100 μmol litre-1
W
THYMOL 100 μmol litre-1

abnormal contracture induced by suxamethonium in MHS swine muscle is not a result of the presence of widespread acetylcholine receptors throughout the muscle membrane, and implies that the abnormal response to suxamethonium in MHS muscle is not caused by an effect on nicotinic acetylcholine receptors.

It has been postulated that the abnormal muscle contraction in MHS human and swine muscle is a result of an increase of Ca^{2+} concentration in the myoplasm (Kalow et al., 1970; Moulds and Denborough, 1974). Two mechanisms for the increased calcium concentration in the myoplasm may be involved. One is the release of Ca^{2+} from SR, the other being a direct inflow of Ca^{2+} into the myoplasm from the extracellular fluid (e.c.f.) resulting from a change in membrane permeability. These two mechanisms may be related to one another.

Small amounts of Ca^{2+} can induce the release of larger amounts of Ca^{2+} from the SR (Endo, Tanaka and Ogawa, 1970). The source of this so-called triggering Ca^{2+} might be the sarcolemma, the T-system membrane, the e.c.f. or any combination of these. Depolarization of the sarcolemma and the T-system by suxamethonium or KCl may result in a small amount of Ca^{2+} being released from the membranes. This small amount of Ca^{2+} may not be sufficient to activate directly the contractile proteins. However, it may act as a trigger to release more Ca^{2+} from the SR by the Ca^{2+}-induced Ca^{2+} release mechanism. The observation in the present investigation that the contractures usually caused by suxamethonium and KCl in MHS muscle do not occur in glycerinated MHS fibres suggests that in MH there may be defects in the sarcolemma and the T-system, resulting in excess Ca^{2+} release from the membrane or increased Ca^{2+} inflow from e.c.f.

In normal muscle Ca^{2+} which enters the myoplasm from e.c.f. does not induce muscle contracture. This influx of Ca^{2+} results in a concentration of intracellular Ca^{2+} of 3 µmol $litre^{-1}$ per action potential, which is insufficient to induce muscle contraction. The Ca^{2+} capacity of the contractile proteins is about 50 µmol $litre^{-1}$, which is greater than the increase of intracellular Ca^{2+} concentration (Endo, 1977).

Caffeine and halothane may enhance the Ca^{2+}-induced Ca^{2+} release mechanism and also lower the threshold of Ca^{2+} release from SR (Endo, 1977). The abnormal contractures which occur in MHS muscle in response to halothane, caffeine and thymol may be induced by these mechanisms as caffeine (Endo, Tanaka and Ogawa, 1970), halothane (Endo, 1977) and thymol (Ogawa, 1970) have all been shown to release Ca^{2+} from SR.

In the present investigation dantrolene sodium was effective in reversing contractures induced in MHS muscle by halothane, caffeine, suxamethonium and thymol. Dantrolene sodium significantly inhibited the halothane and suxamethonium contractures in MHS muscle, and D_2O completely inhibited contractures induced in MHS muscle by any of the five drugs. This suggests that in MHS muscle there may be abnormalities in the excitation–contraction coupling mechanism or in the SR and in the sarcolemma and the T-system.

REFERENCES

Auerbach, A., and Betz, W. (1971). Does curare affect transmitter release? *J. Physiol. (Lond.)*, **213**, 691.

Axelsson, J., and Thesleff, S. (1959). A study of supersensitivity in denervated mammalian skeletal muscle. *J. Physiol. (Lond.)*, **147**, 178.

Eisenberg, B., and Eisenberg, R. S. (1968). Selective disruption of the sarcotubular system in frog sartorius muscle. *J. Cell Biol.*, **39**, 451.

Ellis, K. O., and Carpenter, J. F. (1972). Studies on the mechanism of action of dantrolene sodium. *Naunyn Schmiedebergs Arch. Pharmacol.*, **275**, 83.

Endo, M. (1977). Calcium release from the sarcoplasmic reticulum. *Physiol. Rev.*, **57**, 71.

—— Tanaka, M., and Ogawa, W. (1970). Calcium-induced release of calcium from the sarcoplasmic reticulum of skinned skeletal muscle fibres. *Nature (Lond.)*, **228**, 34.

Fujino, M., Yamaguchi, T., and Suzuki, K. (1961). Glycerol effect and the mechanism linking excitation of plasma membrane with contraction. *Nature (Lond.)*, **192**, 1159.

Gutman, E., and Sandow, A. (1965). Caffeine-induced contracture and potentiation of contraction in normal and denervated rat muscle. *Life Sci.*, **4**, 1149.

Howell, J. N., and Jenden, D. J. (1967). T-tubules of skeletal muscle: morphological alterations which interrupt excitation–contraction coupling. *Fed. Proc.*, **26**, 553.

Kalow, W., Britt, B. A., Terreau, M. E., and Haist, C. (1970). Metabolic error of muscle metabolism after recovery from malignant hyperthermia. *Lancet*, **2**, 895.

Kaminer, B. (1960). Effect of heavy water on different types of muscle and glycerol extracted psoas fibres. *Nature (Lond.)*, **185**, 172.

Koelle, G. B. (1975). *The Pharmacological Basis of Therapeutics*, 5th edn (eds L. S. Goodman and A. Gilman), p. 575. New York: Macmillan.

Miledi, R. (1960). The acetylcholine sensitivity of frog muscle fibres after complete or partial denervation. *J. Physiol. (Lond.)*, **151**, 1.

Moulds, R. F. W. (1978). *Second International Congress on Malignant Hyperthermia*, p. 49, New York: Grune and Stratton.

—— Denborough, M. A. (1974). Biochemical basis of malignant hyperpyrexia. *Br. Med. J.*, **2**, 241.

Ogawa, Y. (1970). Some properties of fragmented frog sarcoplasmic reticulum with particular reference to its response to caffeine. *J. Biochem.*, **67**, 667.

Okumura, F., Crocker, B., and Denborough, M. A. (1979). Identification of susceptibility to malignant hyperpyrexia in swine. *Br. J. Anaesth.*, **51**, 171.

Putney, J. W. jr, and Bianchi, C. P. (1974). Site of action of dantrolene in frog sartorius muscle. *J. Pharmacol. Exp. Ther.*, **189**, 202.

Rosenblueth, A., and Luco, J. V. (1937). A study of denervated mammalian skeletal muscle. *Am. J. Physiol.*, **120**, 781.

Thesleff, S. (1974). Physiological effects of denervation of muscle. *Ann. N.Y. Acad. Sci.*, **228**, 89.

SITE DE L'ANOMALIE DE LA CELLULE MUSCULAIRE CHEZ UN PORC SUSCEPTIBLE A L'HYPERPYREXIE MALIGNE

RESUME

Des études effectuées *in vitro*, à l'aide d'agents qui agissent spécifiquement sur les différentes parties du mécanisme contractile du muscle, laissent penser que l'anomalie du muscle chez les porcs susceptibles à l'hyperpyrexie maligne (MHS) est distale de la membrane post-jonctionale et qu'elle n'est pas le résultat des récepteurs d'acétylcholine étendus sur l'ensemble de la membrane musculaire. Deux sites possibles sont mis en cause, l'un étant le sarcolemme et le système en T, l'autre le mécanisme de couplage excitation–contraction et le réticulum du sarcoplasme.

STUDIEN DER ABNORMALITÄT VON MUSKELZELLEN BEI SCHWEINEN, DIE ANFÄLLIG AUF HYPERTHERMIE SIND

ZUSAMMENFASSUNG

In vitro-Studien mit Mitteln, die spezifisch auf verschiedene Teile des Muskelkontraktionsmechanismus' wirken, zeigten, dass die Abnormalität der Muskeln von Schweinen, die auf maligne Hyperpyrexie (MHS) anfällig sind, distal zur postjunktionalen Membrane liegt, und kein Resultat der durch die gesamte Muskelmembrane verbreiteten Azetylcholin-Rezeptoren ist. Zwei mögliche Stellen gibt es—die eine ist das Sarkolemm und das T-System, die andere der Erregungs/Kontraktions-Kopplungsmechanismus und das Sarkoplasma-Reticulum.

SITIO DE ANORMALIDAD CELULAR DEL MUSCULO DE UN CHANCHO SUSCEPTIBLE A HIPERTERMIA MALIGNA

SUMMARIO

A raíz de estudios *in vitro* en los cuales se usaron agentes que actúan específicamente en distintas partes del mecanismo de contracción del músculo, se sugiere que la anormalidad en la hiperpirexia maligna susceptible (HMS) del músculo del chancho se ubica distal de la membrana postjuntura y que no resulta de la dispersión de receptores de acetilcolina en todas partes de la membrana del músculo. Dos lugares posibles se hallan involucrados, uno siendo el sarcolema y el sistema "T", y el otro el mecanismo de acoplamiento contracción-excitación y el retículo sarcoplásmico.

Br. J. Anaesth. (1980), **52**, 385

RESPONSE OF MHS SWINE TO I.V. INFUSION OF LIGNOCAINE AND BUPIVACAINE

G. G. HARRISON AND D. F. MORRELL

SUMMARY

We report the negative response of MHS swine to i.v. infusions of lignocaine and bupivacaine yielding plasma concentrations which equal or exceed those reported in humans during extradural analgesia. It is concluded that local anaesthetic techniques using the amide-linked local anaesthetics administered in conventional dosage are safe to use in patients known to be genetically susceptible to malignant hyperthermia.

While it is accepted that the anaesthetic technique of lowest risk for the patient known to be genetically susceptible to malignant hyperthermia is some form of regional or local analgesia, strictures against the use of the amide-linked group of anaesthetic drugs (lignocaine and bupivacaine) are still voiced (Britt, 1973; Britt, Kwong and Endrenyi, 1977a; Relton, Britt and Steward, 1973; Strobel, 1977).

Such strictures are based on the work of Bianchi and others which demonstrated that lignocaine, in contrast to procaine and other ester-linked tertiary amine local anaesthetics, potentiated caffeine and caffeine/halothane induced contractures of muscle *in vitro*, enhancing also the oxygen uptake of such preparations (Bianchi and Boulton, 1967; Novotny and Bianchi, 1967; Bianchi, 1968; Strobel and Bianchi, 1971).

Clinical evidence cited in support of such strictures is scant and consists of "unpublished data" and "personal communication" reporting rare incidents of putative initiation of malignant hyperthermia by the administration of amide-linked anaesthetics to MHS individuals (Kalow et al., 1970; Britt, Kwong and Endrenyi, et al., 1977b).

In many hospitals today, the most readily available local anaesthetic drugs are usually members of the amide-linked group—lignocaine, mepivacaine and bupivacaine. This circumstance, and the fact that the concentration of lignocaine which produced potentiation of caffeine induced muscle rigor *in vitro*, was about 100-fold greater than the convulsive threshold *in vivo* in man (Foldes et al., 1960; Sasyniuk and Ogilvie, 1975), and was so greatly in excess of concentrations likely to be found systemically after conventional clinical use, stimulated us to examine the validity of these strictures against the use of such local anaesthetics in the MHS patient. We used the MHS Landrace pig as the experimental model.

We report here the response of MHS Landrace swine to the i.v. infusion of lignocaine and bupivacaine in doses which produced serum concentrations equal to and greater than those reported in humans following extradural and other major regional blocks or topical analgesia of the larynx.

METHODS

Four MHS Landrace swine, screened and identified as described previously (Harrison, 1977), were used in this investigation. The reactions of these animals were observed in response to the infusion of lignocaine on 10 occasions (two pigs three times, two pigs twice) and bupivacaine on eight occasions (four pigs twice). Subsequently, each pig was submitted to a confirmatory halothane challenge.

The plan for each infusion was as follows:

Anaesthesia was induced with thiopentone administered via an ear vein, the trachea was intubated and anaesthesia was maintained with nitrous oxide in oxygen administered by intermittent positive pressure ventilation using a Manley ventilator. When necessary, supplementary doses of thiopentone were administered. Body temperature was recorded from the probe of an Electric Universal Thermometer (TE3, ELLAB, Denmark) placed deep in the medial muscle mass of the thigh. A catheter was introduced into a jugular vein via a cut-down in the neck and advanced to the level of the right atrium. This catheter served for blood sampling and for the i.v.

G. G. HARRISON, M.D., F.F.A.R.C.S. (ENG.); D. F. MORRELL, M.B., CH.B., F.F.A.(S.A.); Department of Anaesthetics, University of Cape Town, South Africa.

0007–0912/80/040385–03 $01.00

© Macmillan Journals Ltd 1980

administration of drugs. Blood samples (mixed venous blood) from this site were analysed for:

(1) Acid–base studies at 2, 5, 10, 15 and 30 min after local anaesthetic infusion (interpolation technique).

(2) Plasma concentrations of lignocaine/bupivacaine at 2, 5, 10, 15 and 30 min after infusion. Lignocaine and bupivacaine were assayed by the gas–liquid chromatographic method of Tucker (1970). A calibration curve with standard solutions was prepared from a blank specimen for each pig on each occasion. Using cyclizine hydrochloride as an internal standard and with quantitation by peak height ratios correlation coefficients were consistently greater than 0.998. (Pye Unicam GCV Chromatograph with dual FID and DP88 computing integrator using 2.1-m columns packed with 5% OV101.)

The test drugs, lignocaine and bupivacaine, were administered as follows: *Lignocaine*—initial dose 1.5 mg kg^{-1} followed by infusion of 30 μg kg^{-1} min^{-1} in initial experiments, increased in later experiments to 2–3 mg kg^{-1} and 120 μg kg^{-1} min^{-1}. *Bupivacaine* —1 mg kg^{-1} administered over 5–10 min.

In view of the importance of the free base form of the anaesthetic to its contracture-producing ability (Bianchi, 1968), we deliberately induced severe metabolic alkalosis in two test animals by infusions of sodium bicarbonate 4.2% in addition to the routine use of hyperventilation.

Criteria of the malignant hyperthermic syndrome sought included onset of muscle rigor resulting in characteristic extension of hind legs (Harrison, 1975); supraventricular tachycardia; rapid progressive increase in muscle temperature; and metabolic acidosis.

RESULTS

No sign of the onset of malignant hyperthermia syndrome was observed in any animal in response to the i.v. infusion of lignocaine or bupivacaine.

The plasma concentrations of lignocaine and bupivacaine assayed during infusion are recorded in figure 1. Mixed venous pH values during the majority of infusions (13) were in the range 7.4–7.5. The ranges 7.5–7.6 and 7.6–7.7 were noted in two infusions each, and 7.2–7.3 in one.

At the conclusion of the experiment all animals, when exposed to halothane, developed MHS syndrome to an extent which required treatment with dantrolene i.v. to ensure their survival.

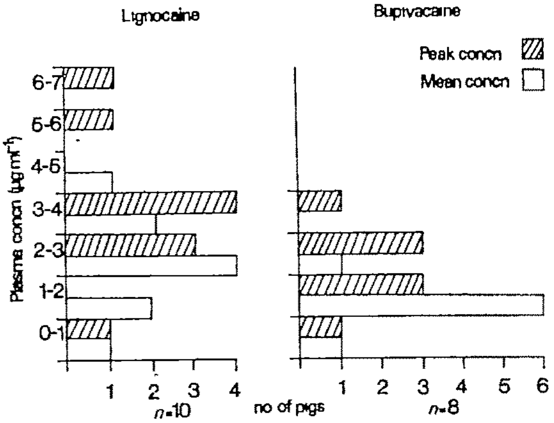


FIG. 1. Peak and mean plasma lignocaine and bupivacaine concentrations observed following i.v. infusion.

DISCUSSION

When local anaesthetic techniques are used, with the notable exception of bilateral intercostal nerve blocks, the greatest plasma concentrations of local anaesthetic drugs are recorded in association with extradural anaesthesia.

In the case of lignocaine, concentrations from 2.4 μg ml^{-1} (Tucker and Mather, 1975) to 4.5 μg ml^{-1} (Covino and Vassallo, 1976) are reported. With bupivacaine, plasma concentrations reported range from the former authors' report of 0.7 μg ml^{-1} to 1.49 μg ml^{-1} reported by Moore and others (1976). Exposure of MHS swine to such circulating concentrations and greater failed to evoke any untoward response. Our findings, considered with the lack of well-documented human cases of malignant hyperthermia provoked by lignocaine or bupivacaine, cast doubts on the validity of the strictures advocated on the use of the amide-linked group of local anaesthetic drugs in patients known to be susceptible to malignant hyperthermia, and suggest that these drugs may be safe when given in conventional clinical dosage.

ACKNOWLEDGEMENTS

MHS pigs were supplied by the J. S. Marais Laboratory of the Department of Surgery of the University of Cape Town and financial support came from Sterling Winthrop S.A. (Pty) Ltd. Assays were performed by Jeanne Meyer.

REFERENCES

Bianchi, C. P. (1968). Pharmacological action on excitation–contraction coupling in striated muscle. *Fed. Proc.*, **27**, 126.

—— Boulton, T. C. (1967). Action of local anaesthetics on coupling systems in muscle. *J. Pharmacol. Exp. Ther.*, **157**, 388.

Britt, B. A. (1973). Prevention of malignant hyperthermia; in *International Symposium on Malignant Hyperthermia* (eds R. Gordon, B. A. Britt and W. Kalow), p. 451. Springfield: Charles Thomas.

—— Kwong, F. H., and Endrenyi, L. (1977a). The management of the MHS patient; in *Malignant Hyperthermia—Current Concepts* (ed. E. O. Henschel), p. 63. New York: Appleton-Crofts.

—— —— —— (1977b). The clinical and laboratory features of malignant hyperthermia; in *Malignant Hyperthermia—Current Concepts* (ed. E. O. Henschel), p. 9. New York: Appleton-Crofts.

Covino, B., and Vassallo, H. G. (1976). *Local Anaesthetics—Mechanisms of Actions and Clinical Use.* p. 97. New York, San Francisco and London: Grune and Stratton.

Foldes, F. F., Malloy, R., Minall, P. G., Koukal, C. R., and Pearl, M. B. (1960). Comparison of toxicity of intravenously given local anesthetic agents in man. *J.A.M.A.*, **172,** 1493.

Harrison, G. G. (1975). Control of the hyperpyrexic syndrome in MHS swine by dantrolene sodium. *Br. J. Anaesth.*, **47,** 62.

—— (1977). The prophylaxis of malignant hyperthermia by oral dantrolene sodium in MHS swine. *Br. J. Anaesth.*, **49,** 315.

Kalow, W., Britt, B. A., Terreau, M. E., and Haist, C. (1970). Metabolic error of muscle metabolism after recovery from malignant hyperthermia. *Lancet,* **2,** 895.

Moore, D. C., Mather, L. E., Bridenbaugh, P. O., Bridenbaugh, L. D., Balfour, R. I., Lysons, D. F., and Horton, W. G. (1976). Arterial and venous plasma levels of bupivacaine following epidural and intercostal block. *Anesthesiology*, **45,** 34.

Novotny, I., and Bianchi, C. P. (1967). The effect of xylocaine on O_2 consumption of frog sartorius muscle. *J. Pharmacol. Exp. Ther.*, **155,** 456.

Relton, J. E. S., Britt, B. A., and Steward, D. J. (1973). Malignant hyperpyrexia. *Br. J. Anaesth.*, **45,** 269.

Sasyniuk, B. I., and Ogilvie, R. I. (1975). Anti-arrhythmic drugs—electrophysiological and pharmacological considerations. *Ann. Rev. Pharmacol.*, **15,** 131.

Strobel, G. (1977). Calcium, muscle and malignant hyperthermia; in *Malignant Hyperthermia—Current Concepts* (ed. E. O. Henschel), p. 99. New York: Appleton-Crofts.

—— Bianchi, C. P. (1971). An *in vitro* model of anesthetic hypertonic pyrexia, halothane-caffeine induced muscle contracture. *Anesthesiology*, **35,** 465.

Tucker, G. T. (1970). Determination of bupivacaine and other anilide-type local anesthetics in human blood and plasma by gas chromatography. *Anesthesiology,* **32,** 255.

—— Mather, L. E. (1975). Pharmacokinetics of local anaesthetic agents. *Br. J. Anaesth.*, **47,** 213.

REACTION DE PORCS SUSCEPTIBLES A L'HYPERPYREXIE MALIGNE A UNE INFUSION INTRAVEINEUSE DE LIGNOCAINE ET DE BUPIVACAINE

RESUME

Nous signalons dans cet article la réaction négative de porcs susceptibles à l'hyperpyrexie maligne (MHS), aux infusions de lignocaïne et de bupivacaïne entraînant des concentrations dans le plasma équivalentes ou supérieures à celles signalées chez les humains pendant une analgésie extradurale. On en a conclu que les techniques d'anesthésie locale basées sur les agents anesthésiants locaux de la classe des amides peuvent être administrés sans danger et aux doses habituelles aux patients que l'on sait être génétiquement susceptibles à l'hyperthermie maligne.

REAKTION VON MHS-SCHWEINEN AUF INTRAVENÖSE INFUSION VON LIGNOCAIN UND BUPIVACAIN

ZUSAMMENFASSUNG

Wir berichten über die negative Reaktion von MHS (anfällig auf maligne Hyperprexie)-Schweinen auf intravenöse Infusionen von Lignocain und Bupivacain in Plasmakonzentrationen, die diejenigen erreichen oder übertreffen, die bei Menschen während extraduraler Analgesie gemeldet werden. Es wird geschlossen, dass Lokalanasthesiemethoden, bei denen amidhältige lokale Betäubungsmittel in konventionellen Dosen verwendet werden, gefahrlos bei Patienten angewendet werden können, die genetisch auf maligne Hyperthermie anfällig sind.

RESPUESTA DE CHANCHOS CON HMS A INFUSIONES I.V. DE LIGNOCAINA Y DE BUPIVACAINA

SUMARIO

Informamos sobre la respuesta negativa del chancho con HMS a infusiones i.v. de lignocaina y de bupivacaina que tuvieron por resultado concentraciones en el plasma iguales o mayores de las registradas en seres humanos durante la analgesia extradural. Se llega a la conclusión de que las técnicas de anestesia local mediante agentes anestéticos locales del grupo de las ámidas administrados según dosis convencionales pueden usarse en toda seguridad en pacientes conocidos por ser susceptibles genéticamente a la hipertermia maligna.

Br. J. Anaesth. (1980), **52** 389

HALF-LIFE OF ANGIOTENSIN II IN THE CONSCIOUS AND BARBITURATE-ANAESTHETIZED RAT

B. J. CHAPMAN, D. P. BROOKS AND K. A. MUNDAY

SUMMARY

The half-life ($T_{\frac{1}{2}}$) of angiotensin II was measured in rats with chronic indwelling catheters. In conscious animals $T_{\frac{1}{2}}$ was 14.8 ± 2.5 s; during anaesthesia $T_{\frac{1}{2}}$ increased by 60%. Anaesthesia decreased the control arterial pressure, but did not alter the sensitivity to injected angiotensin II. The causes and consequences of this change in angiotensin catabolism are discussed.

It is well known that barbiturate anaesthesia can cause significant changes in the cardiovascular and renin–angiotensin systems. For example, cardiac output, arterial pressure and the blood flows to most organs decrease (Price, 1960); plasma renin activity increases (Pettinger et al., 1975; Pettinger, 1978); the renal response to infused angiotensin II may be reversed (Navar and Langford, 1974); and the pressor response to angiotensin i.v. may decrease, largely as a result of inhibition of the c.n.s.-mediated component of this response (Dickinson and Ferrario, 1974). Haas and colleagues (1969), however, found that the pressor response to the intra-arterial administration of angiotensin II was enhanced by anaesthesia and they attributed this to an alteration in the retention of angiotensin by peripheral tissues. Therefore, we decided to investigate further the influence of anaesthesia on the rate of removal of angiotensin II using methods that have been developed recently (Al-Merani et al., 1978). Our observation that barbiturate anaesthesia prolongs the half-life ($T_{\frac{1}{2}}$) of angiotensin II in the circulatory system by 60% may have relevance to many studies of the renin–angiotensin system.

METHODS

The conscious rat preparation

Female Wistar rats (250–300 g) were anaesthetized for a brief period with halothane and a nitrous oxide–oxygen mixture. The right carotid artery and jugular vein were cannulated with PP25 polyethylene tubing (Portex). These cannulae were threaded under the skin, exteriorized at the back of the neck and secured by a stitch at this site. The cannulae were filled with heparinized saline (50 i.u. ml^{-1}) and heat-sealed. The incision was sutured and the animals allowed to recover consciousness.

Measurement of $T_{\frac{1}{2}}$ of angiotensin II

Two days after implantation of the catheters, each animal was placed in a restraining cage and the cannulae were flushed with heparinized saline. The venous cannula was connected to a pump for the infusion of angiotensin II (Ciba, Hypertensin) and the arterial cannula connected to an Elcomatic EM750 (Elcomatic, Glasgow) arterial pressure transducer. Arterial pressure was recorded on a Vitatron potentiometric recorder (Fisons).

The half-life of angiotensin II was determined using the methods described in detail by Al-Merani and colleagues (1978). Goldstein, Aranow and Kalman (1968) have shown theoretically and empirically that the plasma concentration of any hormone (or drug) is proportional to the dose administered; this is called the "plateau principle". Thus, any given infusion of angiotensin II (x ng min^{-1}) will result in a plasma concentration C ng/ml of plasma of the hormone, and a pressor response R' mm Hg. If twice the dose of angiotensin II is injected ($2x$ ng min^{-1}), the peak concentration of angiotensin II will be $2C$ ng ml^{-1}, with a pressor response R''. Of course, this pressor response R'' will not necessarily equal $2 \times R'$. As angiotensin II is catabolized after the infusion is stopped, the concentration in the plasma will decrease exponentially. When the pressor response has decreased from R'' to R' the concentration in the plasma must have decreased from $2C$ to C, and the elapsed time must equal the half-life of the hormone. The application

---

B. J. CHAPMAN, B.SC., PH.D.; D. P. BROOKS, B.SC., M.SC., PH.D.; K. A. MUNDAY, B.SC., PH.D., F.I. BIOL.; Department of Physiology and Pharmacology, School of Biochemical and Physiological Sciences, University of Southampton, Bassett Crescent East, Southampton SO9 3TU.

0007-0912/80/040389-05 $01.00

© Macmillan Journals Ltd 1980

of this method to the measurement of $T_{\frac{1}{2}}$ of angiotensin has been validated by Al-Merani and coworkers (1978).

Thus changes in the plasma concentration of angiotensin II were deduced from studies of the rate of change of arterial pressure following the responses to infused doses of angiotensin II. For each animal a graph was constructed for various infusions of angiotensin II (10–1000 ng kg^{-1} min^{-1}), showing the relationship between the plateau increase of arterial pressure and the concentration of angiotensin II in the plasma. This concentration of angiotensin II is proportional to the rate of infusion of angiotensin and can, therefore, be quantified in terms of the infusion rate. By reference to this graph, changes in the plasma concentration of angiotensin could be deduced (without taking blood samples) by examining the downsweep of the arterial pressure recording obtained when an infusion of angiotensin was stopped suddenly.

The $T_{\frac{1}{2}}$ of angiotensin was determined whilst each animal was conscious. In some animals, anaesthesia was induced with sodium pentobarbitone 60 mg kg^{-1} i.p. (Sigma) and 30 min later $T_{\frac{1}{2}}$ of the hormone was redetermined. In a group of control animals anaesthesia was not induced, and two $T_{\frac{1}{2}}$ determinations were made 30 min apart. Thus, the whole procedure was repeated twice in each animal: two graphs were constructed showing change in arterial pressure *v.* dose of angiotensin II infused, so that any effect of anaesthesia upon this relationship cannot influence $T_{\frac{1}{2}}$ determination.

The results are reported as the mean ± SEM and were evaluated by Student's *t* test as described by Colquhoun (1971).

RESULTS

In seven rats, the half-life of angiotensin II was 14.8 ± 2.5 s when the animals were conscious. This increased to 23.5 ± 3.5 s 30 min after the induction of barbiturate anaesthesia ($P < 0.05$). Thus, the half-life increased by 59% (fig. 1A). In four control animals $T_{\frac{1}{2}}$ of angiotensin was initially 14.2 ± 1.9 s; this was not significantly different from the initial value obtained for the first group of rats ($P > 0.05$). Thirty minutes later $T_{\frac{1}{2}}$ was redetermined with the animals still conscious, as 12.3 ± 1.4 s; this value was not significantly different from the initial measurement in this group ($P > 0.05$) but was significantly less than the value obtained from the anaesthetized rats ($P < 0.05$).

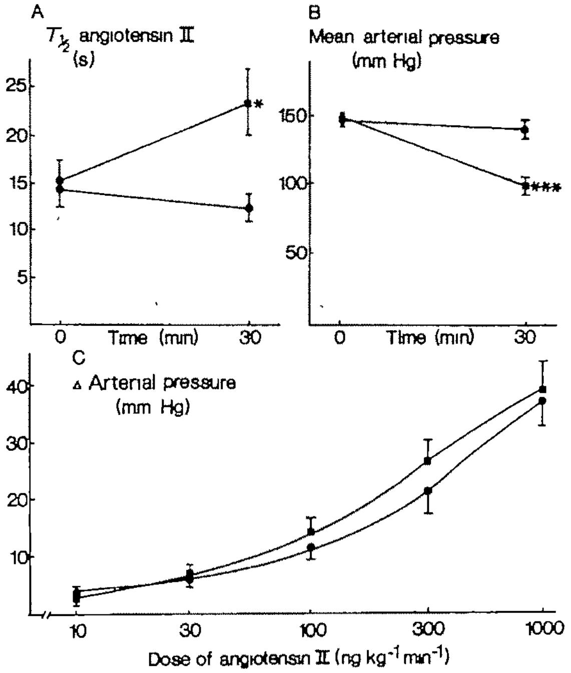


FIG. 1. A: $T_{\frac{1}{2}}$ of angiotensin II in the rat, measured at two times. All rats were conscious for the first measurement; for the second measurement seven rats were anaesthetized, four were not anaesthetized. ● = conscious; ■ = anaesthetized (*$P < 0.05$). B: Basal mean arterial pressure in the same two groups of rats. (*** $P < 0.001$). C: Increases in mean arterial pressure caused by various doses of injected angiotensin II in four conscious (●) and seven anaesthetized (■) rats.

In the seven experimental rats, anaesthesia reduced arterial pressure from 146 ± 3 to 100 ± 8 mm Hg ($P < 0.001$); in the four control animals the arterial pressure remained almost constant, being 143 ± 3 initially and 139 ± 6 mm Hg 30 min later (fig. 1B).

Fig. 1C shows the average values of the plateau arterial pressure increases for each infusion of angiotensin II; the small differences between the two lines were not significant ($P > 0.05$).

DISCUSSION

The methods used here to determine $T_{\frac{1}{2}}$ of angiotensin II have previously been tested extensively, and found to give valid results (Al-Merani et al., 1978). The values obtained for $T_{\frac{1}{2}}$ of angiotensin II (12–25 s) are much smaller than values reported by most other workers, most of whom have used radioimmunoassay methods to determine angiotensin II concentrations (Ryan, 1974; Ledingham and Leary, 1974). Ryan (1974) has suggested that radioimmunoassay methods probably detected the breakdown products of angiotensin catabolism and, therefore, underestimate the rate of angiotensin breakdown, a view supported by the measurements of Caravaggi and colleagues (1976). Our control values for $T_{\frac{1}{2}}$ of angiotensin agree closely with those of Hodge, Ng and Vane (1967) who used bioassay methods to measure the abilities of various organs of the dog to destroy angiotensin II, and deduced $T_{\frac{1}{2}}$ of 15 s.

There is a possible objection to the methods employed in the present study. The relationship between the dose of angiotensin and the plateau pressor response is defined experimentally, and is shown in figure 1c. However, this graph might not show the relationship between dose and arterial pressure when the angiotensin concentration is decreasing, particularly if the arterial pressure response disappears only slowly at a time when the angiotensin is decreasing rapidly. Thus the methods employed here might measure $T_{\frac{1}{2}}$ of the arterial pressure *response*, not $T_{\frac{1}{2}}$ of the hormone *causing* the arterial pressure response. Al-Merani and colleagues (1978) have established that this objection is not true and does not invalidate these methods. Angiotensin II was infused into rats until a steady increase in arterial pressure was obtained; in some instances the infusion of angiotensin II was switched off and the initial rate of decrease of arterial pressure was measured; in other instances the infusion of angiotensin II was maintained, but a large dose of saralasin was injected (saralasin blocks the angiotensin II receptors and thus prevents the angiotensin II from inducing its response) and the rate of decrease of arterial pressure was measured. Saralasin caused the arterial pressure to decrease more than twice as rapidly as did switching off the angiotensin II infusion. Thus the pressor response can easily change fast enough to indicate accurately the alterations in the concentration of angiotensin II.

Anaesthesia increased $T_{\frac{1}{2}}$ of angiotensin by 60%. Information in the literature leads to the conclusion that this change is probably the result of a combination of two phenomena: a decrease in the delivery of angiotensin to the sites of catabolism, and a decrease in the activity of the enzymes responsible for angiotensin catabolism. Angiotensin catabolism occurs predominantly in the capillary beds of most tissues other than lung, and occurs only slowly in the blood (Hodge, Ng and Vane, 1967). Barbiturate anaesthesia is known to decrease the blood flows through most tissues and hence cardiac output (Price, 1960). The decrease in cardiac output which follows barbiturate anaesthesia in the rat is reported to be between 20 and 30% (Popovic and Kent, 1964; Dawson, Nadel and Horvath, 1968). Thus, the delivery of angiotensin II to the sites of angiotensin catabolism must decrease also, and should contribute significantly to the increased $T_{\frac{1}{2}}$ of angiotensin II. The enzymes in the peripheral capillary beds, which are responsible for angiotensin catabolism, are membrane-bound (Ryan, 1974; Lafontaine, Nivez and Ardaillon, 1979). There is no direct evidence showing how angiotensinases are affected by barbiturates, but it is known that barbiturates dissolve in cell membranes, alter their physical properties (Lee, 1976) and increase the activity of some membrane-bound enzymes (Conney, 1967), although decreasing the activity of others (Hertz, 1977). It has been shown, however, that anaesthesia can decrease the removal of angiotensin by peripheral capillary beds (Haas et al., 1969) and this must also contribute to the increased $T_{\frac{1}{2}}$ of angiotensin II. The studies of Haas and co-workers (1969) suggest that plasma contains a factor which inhibits the retention of angiotensin by peripheral capillary beds, but these studies did not determine whether anaesthesia altered the circulating concentration of this factor.

A decrease in the rate of angiotensin catabolism should increase plasma concentrations of angiotensin. The observations of Miller, Longneck and Peach (1978) are in agreement with this since they have obtained evidence for enhanced angiotensin activity in anaesthetized animals when the renin concentrations were unaltered. Most workers find that anaesthesia leads to increased plasma renin activity (Pettinger, 1978). Thus, very great circulating concentrations of angiotensin should be expected in anaesthetized animals.

The pressor responsiveness to angiotensin II was not altered significantly by anaesthesia in our experiments. There may be a number of factors which could change the sensitivity to angiotensin during anaesthesia, but these do not all act in the same direction. Dickinson and Ferrario (1974) found that barbiturate anaesthesia decreases the pressor response to angiotensin (especially when the angiotensin is injected into the arterial supply to the brain) by inhibiting a central nervous system component of the pressor response. However, our results show that barbiturate anaesthesia slows the rate of angiotensin II catabolism, so that any given rate of angiotensin infusion will cause a greater arterial concentration of the hormone and will, therefore, tend to cause a greater stimulation of all of the components of the pressor response; a similar conclusion has been reached by Haas and colleagues (1969).

Angiotensin II can have two actions on kidney function. Small doses cause a sustained sodium retention, while large doses have a biphasic action, initially causing sodium retention which fades after a short time to give way to enhanced sodium excretion. There is evidence to show that the sodium retention and sodium excretion are mediated by independent mechanisms (Brooks, Chapman and Munday, 1979); the sodium retention with small and large doses of angiotensin II is probably dependent on the renal vasoconstrictor action of angiotensin II, while the sodium excreting action seen with a large dose of angiotensin II is probably caused by inhibition of sodium reabsorption (Navar and Langford, 1974). There is evidence that anaesthesia can alter the response to angiotensin: a dose of angiotensin II which causes only sodium retention in a conscious animal causes the biphasic response expected of a large dose in an anaesthetized animal (Navar and Langford, 1974). The present studies may help to explain this. Anaesthesia decreases angiotensin breakdown and a greater concentration of angiotensin must circulate in the plasma causing a greater stimulation of the sodium-excreting mechanisms; anaesthesia may also decrease the pressor and vasoconstrictor actions of angiotensin II and may attenuate the sodium-retaining actions of the hormone.

Anaesthesia is known to induce many interrelated changes in the renin–angiotensin system. The present studies, showing that anaesthesia prolongs $T_{\frac{1}{2}}$ of angiotensin in the circulation, may help to clarify some of these changes.

REFERENCES

Al-Merani, S. A. M. A., Brooks, D. P., Chapman, B. J., and Munday, K. A. (1978). The half-lives of angiotensin II, angiotensin II-amide, angiotensin III, Sar^1-Ala^8-angiotensin II and renin in the circulatory system of the rat. *J. Physiol. (Lond.)*, **278**, 471.

Brooks, D. P., Chapman, B. J., and Munday, K. A. (1979). The effect of meclofenamate on the natriuretic and anti-natriuretic actions of angiotensin II in the rat. *J. Physiol. (Lond.)*, **287**, 41P.

Caravaggi, A. M., Bianchi, G., Brown, J. J., Lever, A. F., Morton, J. J., Powell-Jackson, J. D., Robertson, J. I. S., and Semple, P. F. (1976). Blood pressure and plasma angiotensin II concentration after renal artery constriction and angiotensin infusion in the dog. *Circ. Res.*, **38**, 315.

Colquhoun, D. (1971). *Lectures on Biostatistics*. Oxford: Clarendon.

Conney, A. H. (1967). Pharmacological implications of microsomal enzyme inductions. *Pharmacol. Rev.*, **19**, 317.

Dawson, C. A., Nadel, E. R., and Horvath, S. M. (1968). Cardiac output in the cold stressed swimming rat. *Am. J. Physiol.*, **213**, 320.

Dickinson, C. J., and Ferrario, C. M. (1974). Central neurogenic effects of angiotensin; in *Angiotensin* (eds I. H. Page and F. M. Bumpus), p. 408. Berlin, Heidelberg, New York: Springer-Verlag.

Goldstein, A., Aranow, L., and Kalman, S. M. (1968). *Principles of Drug Action: The Basis of Pharmacology*. New York: Harper & Row.

Haas, E., Goldblatt, H., Lewis, L., and Gipson, E. C. (1969). Angiotensin-protective cofactor. *Am. J. Physiol.*, **217**, 981.

Hertz, L. (1977). Drug induced alterations of ion distribution at the cellular level of the central nervous system. *Pharmacol. Rev.*, **29**, 35.

Hodge, R. L., Ng, N. K. F., and Vane, J. R. (1967). Disappearance of angiotensin from the circulation of the dog. *Nature (Lond.)*, **215**, 138.

Lafontaine, J. J., Nivez, M. P., and Ardaillon, R. (1979). Hepatic binding sites for angiotensin II in the rat. *Clin. Sci.*, **56**, 33.

Ledingham, J. G., and Leary, W. P. P. (1974). Catabolism of angiotensin II; in *Angiotensin* (eds I. H. Page and F. M. Bumpus), p. 111. Berlin, Heidelberg, New York: Springer-Verlag.

Lee, A. G. (1976). Interaction between phospholipids and barbiturates. *Biochem. Biophys. Acta*, **455**, 102.

Miller, E. D., Longnecker, D. E., and Peach, M. J. (1978). The regulatory function of the renin–angiotensin system during general anesthesia. *Anesthesiology*, **48**, 399.

Navar, L. C., and Langford, H. C. (1974). Effects of angiotensin on the renal circulation; in *Angiotensin* (eds I. H. Page and F. M. Bumpus), p. 455. Berlin, Heidelberg, New York: Springer-Verlag.

Pettinger, W. A. (1978). Anaesthetics and the renin–angiotensin–aldosterone axis. *Anesthesiology*, **48**, 393.

—— Tanaka, K., Keeton, K., Campbell, W. B., and Brooks, S. N. (1975). Renin release, an artefact of anaesthesia and its implications in rats. *Proc. Soc. Exp. Biol. Med.*, **148**, 625.

Popovic, U. P., and Kent, K. M. (1964). 120-day study of cardiac output in anesthetised rats. *Am. J. Physiol.*, **207**, 767.

Price, H. L. (1960). General anaesthesia and circulatory homeostasis. *Physiol. Rev.*, **40**, 187.

Ryan, J. W. (1974). The fate of angiotensin II; in *Angiotensin* (eds I. H. Page and F. M. Bumpus), p. 81. Berlin, Heidelberg, New York: Springer-Verlag.

DEMI-VIE DE L'ANGIOTENSINE II CHEZ DES RATS CONSCIENTS ET CHEZ DES RATS ANESTHESIES AUX BARBITURIQUES

RESUME

La demi-vie ($T_{\frac{1}{2}}$) de l'angiotensine II a été mesurée sur des rats ayant des cathéters implantés d'une manière permanente. Sur les animaux conscients, $T_{\frac{1}{2}}$ a été de 14,8 ± 2,5 s; pendant l'anesthésie, $T_{\frac{1}{2}}$ a augmenté de 60%. L'anesthésie a fait

baisser la pression artérielle témoin, mais n'a pas modifié la sensibilité à l'angiotensine II injectée. Les causes et conséquences de cette variation dans le catabolisme de l'angiotensine sont développées dans ce document.

HALBWERTSZEIT VON ANGIOTENSIN II IN WACHEN UND IN MIT BARBITURAT NARKOTISIERTEN RATTEN

ZUSAMMENFASSUNG

Die Halbwertzeit ($T_{\frac{1}{2}}$) von Angiotensin II wurde bei Ratten mit chronisch verpflanzten Kathetern gemessen. $T_{\frac{1}{2}}$ betrug 14,8 ± 2,5 s in wachen Ratten; während der Narkose stieg dieser Wert um 60%. Die Narkose senkte den arteriellen Kontrolldruck, veränderte aber nicht die Empfindlichkeit auf injeziertes Angiotensin II. Gründe und Folgen dieser Veränderungen des Angiotensin-Katabolismus' werden erörtert.

MEDIA-VIDA DE LA ANGIOTENSINA II EN EL RATÓN CONSCIENTE Y EL ANESTESIADO CON BARBITÚRICOS

SUMMARIO

Se llevaron a cabo mediciones de la media-vida ($T_{\frac{1}{2}}$) de la angiotensina II en ratones con sondas permanentes. En los animales conscientes, $T_{\frac{1}{2}}$ era de 14,8 ± 2,5 s; durante la anestesia, $T_{\frac{1}{2}}$ aumentó en un 60%. La anestesia tuvo por efecto de disminuir la presión arterial de control, pero no alteró la sensibilidad a la angiotensina II inyectada. Se discuten de las causas y consecuencias de esta modificación del catabolismo de la angiotensina.

Br. J. Anaesth. (1980), **52**, 395

FUNCTIONAL RESIDUAL CAPACITY AND VENTILATORY PRESSURES DURING POSITIVE-PRESSURE VENTILATION AT HIGH FREQUENCIES

A. JONZON, Z. RONDIO AND G. SEDIN

SUMMARY

The functional residual capacity (FRC) was measured in cats by the nitrogen washout technique during positive-pressure ventilation. Frequencies of 60 and 100 b.p.m. were used with insufflation periods of 20% and 35% of the ventilatory cycle, without and with a positive end-expiratory pressure. The higher frequency combined with the shorter insufflation period gave FRC close to that obtained during spontaneous breathing. The lower frequency and the longer insufflation period always gave greater FRC values. A further increase in FRC of about 23–27% was obtained after application of a positive end-expiratory pressure of 0.5 kPa. Adequate ventilation was achieved with small intratracheal and intrapleural pressures at all settings used.

Alveolar collapse and decreased lung compliance occur frequently in neonatal pulmonary disorders, especially respiratory distress syndrome, and result in an abnormally low functional residual capacity (FRC; Prod'ham et al., 1965). Thus FRC may be less than the closing capacity and cause air-trapping and increased venous admixture (Don, Wahba and Craig, 1972). A decreased FRC is also observed in patients during anaesthesia (Hewlett et al., 1974).

Continuous positive airway pressure (CPAP; Gregory et al., 1971) and positive end-expiratory pressure (PEEP; Ashbaugh et al., 1969; Peters, 1969) used to treat pulmonary disorders in which lung collapse predominates, balance the decreased compliance and restore FRC presumably by re-expanding previously collapsed alveoli.

In studies of high-frequency positive-pressure ventilation (HFPPV) with a small positive end-expiratory pressure, no changes in compliance were observed in anaesthetized dogs (Jonzon et al., 1971). Using a similar pattern of ventilation, Nisbet, Dobbinson and Steward (1974) showed that FRC could be maintained in anaesthetized dogs at values slightly greater than those in conscious dogs. It was therefore of interest to investigate the effects on FRC of different frequencies of insufflation and insufflation periods in high-frequency positive-pressure ventilation, with and without PEEP. For this purpose a ventilator with a small internal volume and a low internal compliance was used (Rondio and Ryterski, 1978; Rondio, 1979).

The aim of this study was to investigate: how FRC is altered when different ventilatory frequencies and different insufflation periods are used in high-frequency positive-pressure ventilation; how FRC is altered by the application of PEEP under these circumstances; the interrelations between FRC and ventilatory pressures; and the effects of the different patterns of ventilation on circulatory pressures and heart rate.

METHODS

Animals and anaesthesia

The experiments were performed on five young, healthy cats of either sex weighing between 2.5 and 2.9 kg (mean weight 2.68 kg). General anaesthesia was induced with chloroform and maintained by intermittent infusions of chloralose (E. Merck AG, G.F.R.).

An endotracheal tube was inserted until its tip lay about 1 cm above the carina. A ligature was tied around the trachea to prevent leakage around the tube. A slow infusion of a 5.5% glucose solution was given continuously. Care was taken to keep the body temperature normal.

Measurements

For measurement of arterial pressure a catheter was introduced through the femoral artery to a position in the thoracic part of the aorta. Central venous pressure was measured through a catheter introduced through the femoral vein and advanced until its tip was at the level of the right atrium.

A. JONZON, M.D.; G. SEDIN, M.D.; Department of Paediatrics, University Hospital, S-750 14 Uppsala, Sweden and Department of Physiology and Medical Biophysics, Biomedical Centre, S-751 23 Uppsala, Sweden. Z. RONDIO, M.D., Department of Anaesthesiology, National Research Institute of Mother and Child, 01-211 Warsaw, Poland.
Correspondence to G. Sedin.

0007-0912/80/040395-08 $01.00

© Macmillan Journals Ltd 1980

The intratracheal pressure was measured through a catheter, the tip of which was placed in the endotracheal tube about 2–3 cm above the carina. The intrapleural pressure was measured through a catheter inserted into the left intrapleural space.

Pressure measurements were made with transducers (SE Labs (EMI) Ltd, U.K.). The heart rate (HR) was measured with an instant heart rate meter (Devices Instr. Ltd, U.K.). A 6-channel medical amplifier was used (Elcomatic, EM 760, U.K.) and recordings were made with an oscillograph (Oscillograph 6608, SE Labs Ltd, U.K.).

A nitrogen analyser (W. E. Collins Inc., U.S.A.) was used for measurement of FRC. Expired gas was collected in a latex-rubber bag (Mischbeutel, E. Jaeger AG, G.F.R.). The expiratory tidal volume was measured with a Krogh spirometer. Arterial Po_2, Pco_2, base excess, HCO_3^- and oxygen saturation were measured in an automatic analyser (ABL 1, Radiometer, Denmark).

Ventilator

A fluidic-operated constant-flow time-cycled ventilator (Relog Infant Respirator G-19, Farum, Poland) was used for ventilating the cats. The ventilation frequency and insufflation period could be set independently. The ventilation frequency could be varied between 50 and 120 b.p.m. by increments of 5 b.p.m. and the insufflation period from 20 to 50% of the ventilatory cycle by increments of 5%. The compliance of the ventilator, patient circuit and humidifier ranged between 0.001 and 0.004 litre kPa^{-1} depending on the ventilator setting (Rondio and Ryterski, 1978). The ventilatory pattern of the ventilator used was not identical to that used in the studies of Jonzon and others (1971), Jonzon, Sedin and Sjöstrand (1973), Nisbet, Dobbinson and Steward (1974) or Eriksson and others (1977).

The flow rate and tidal volume measured with a pneumotachograph (Godart–Statham, Holland) and the airway pressure measured with a transducer (Statham P23Db, U.S.A.) during ventilation of a lung model with the Relog respirator at a ventilatory frequency of 60 b.p.m. and an insufflation period of 35% are shown in figure 1.

Because of the construction of the ventilator, the internal volume differed between different ventilator settings. These volumes were measured for each setting and ranged between 0.138 and 0.241 litre and were taken into consideration in the calculations.

In the present study only two frequencies (60 and 100 b.p.m.) and two settings for insufflation (20 and 35% of the respiratory cycle) were investigated. Experiments using 0.5 kPa PEEP were performed with an insufflation period of 35%.

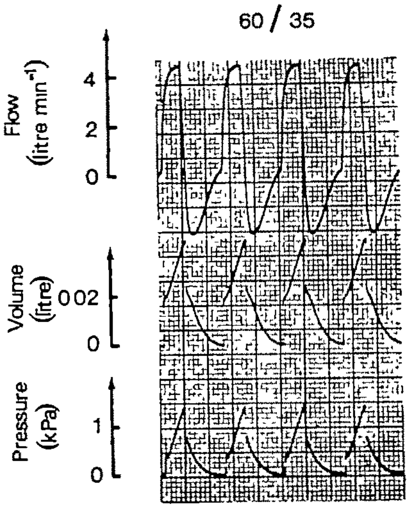


FIG. 1. Experimental recordings of air flow, integrated inspiratory/expiratory volumes and airway pressures obtained with the Relog Infant Respirator G-19 connected to a model lung.

EXPERIMENTAL PROCEDURE

The lungs were ventilated with air at frequencies of 60 and 100 b.p.m. and insufflation periods of 20 and 35% of the ventilatory cycle. The arterial Pco_2 was maintained between 4.5 and 4.7 kPa before the introduction of PEEP. The mean minute volume of expired gas (minute ventilation) was 1.28 litre min^{-1} at a ventilation frequency of 100 b.p.m. and 0.98 litre min^{-1} at a frequency of 60 b.p.m. The minute ventilation was not altered following the addition of PEEP.

The order of experiments was varied between the animals to eliminate the effects of time-related changes in compliance. Before every experimental sequence the arterial acid–base status was determined and corrected if necessary. In every experimental sequence the lung was ventilated with air for at least 10 min and at the end of this period the acid–base variables were measured again. For determination of FRC, ventilation with 100% oxygen was started at end-expiration and simultaneously the collection of expired gas was begun. This was continued for exactly 8 min so that all intrapulmonary and ventilator nitrogen was washed out as determined by the washout curve. The nitrogen concentration of the expired gas (C'_{N_2}) and the expiratory gas volume ($\dot{V}_E$) were measured. FRC was calculated from the following equation:

$$\mathrm{FRC} = \frac{C'_{N_2} \cdot \dot{V}_E}{8.0} - \frac{\text{Measured internal volume}}{\text{of ventilator}} \qquad (1)$$

Measurements of FRC during spontaneous breathing were performed in the same way, using a gas-conditioning system connected to the endotracheal tube with a constant flow of gas through the system at zero pressure.

The arterial pressure, central venous pressure, heart rate, intratracheal pressure and intrapleural pressure were recorded continuously. Intratracheal and intrapleural mean pressures were obtained planimetrically from the recordings.

Results were analysed using Student's *t* test on paired observations.

RESULTS

Functional residual capacity (FRC)

The effects of positive-pressure ventilation on FRC are illustrated in figure 2. Ventilation with PEEP, the slower ventilation frequency (60 b.p.m.) and the longer insufflation period (35%) always produced greater FRC.

At a ventilator frequency of 100 b.p.m. and an insufflation period of 20%, FRC was greater than that during spontaneous breathing and anaesthesia (0.102 litre), but less than that obtained at the same ventilator frequency with an insufflation period of 35% ($P < 0.05$) (fig. 2).

At a ventilatory frequency of 60 b.p.m., the corresponding differences were still clear and statistically significant at the same level ($P < 0.05$). A significantly greater FRC was found when PEEP was applied ($P < 0.05$).

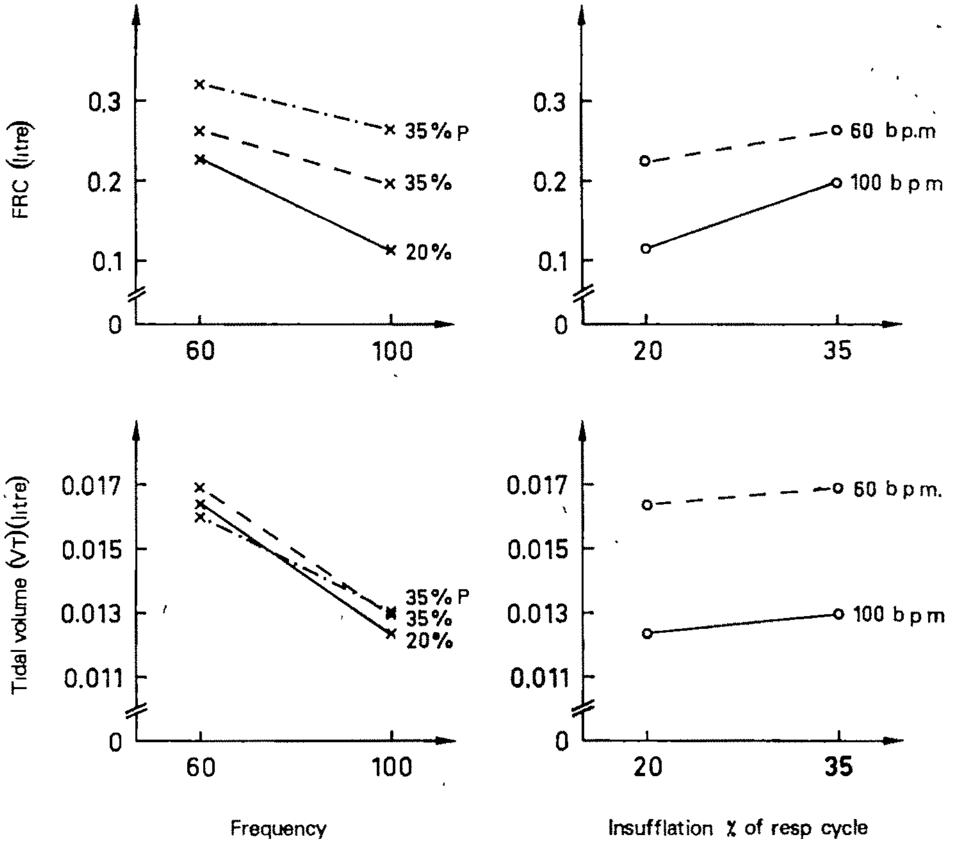


FIG. 2. Functional residual capacity (BTPS) in relation to ventilatory frequency (b.p.m.) and insufflation period (per cent of the ventilatory cycle). Tidal volumes are given in the lower part of the figure (P = ventilation with a positive end-expiratory pressure of 0.5 kPa).

At an insufflation period of 20% of the ventilatory cycle, FRC was greater at a ventilatory frequency of 60 b.p.m. (fig. 2, right side) than at 100 b.p.m. ($P < 0.01$). The same was true at an insufflation period of 35% ($P < 0.05$).

For comparison and interpretation, tidal volumes (V_T) are given in the lower part of figure 2.

Arterial blood-gases

Pa_{CO_2} was almost the same at all settings when no PEEP was used (see experimental procedure). A greater Pa_{CO_2} was noted during ventilation with PEEP than without ($P < 0.01$). When PEEP was applied, Pa_{CO_2} was the same at the two ventilatory frequencies. There were no apparent differences in P_{O_2} in relation to frequency, insufflation period or PEEP.

Ventilatory pressures

The maximum and mean intratracheal pressures did not differ significantly with the ventilatory frequencies used (fig. 3). When PEEP was applied both these pressures were greater.

PEEP of 0.5 kPa also caused greater maximum intrapleural pressures, especially at a ventilatory frequency of 60 b.p.m. (fig. 3, lower part). There were no differences in the maximum and mean intrapleural pressures at the different respiratory settings without PEEP.

Circulatory pressures and heart rate

The central venous pressure (fig. 4, left side) was always greater at a ventilatory frequency of 100 b.p.m. than at 60 b.p.m. ($P < 0.05$). At both frequencies the application of 0.5 kPa PEEP caused an increase in

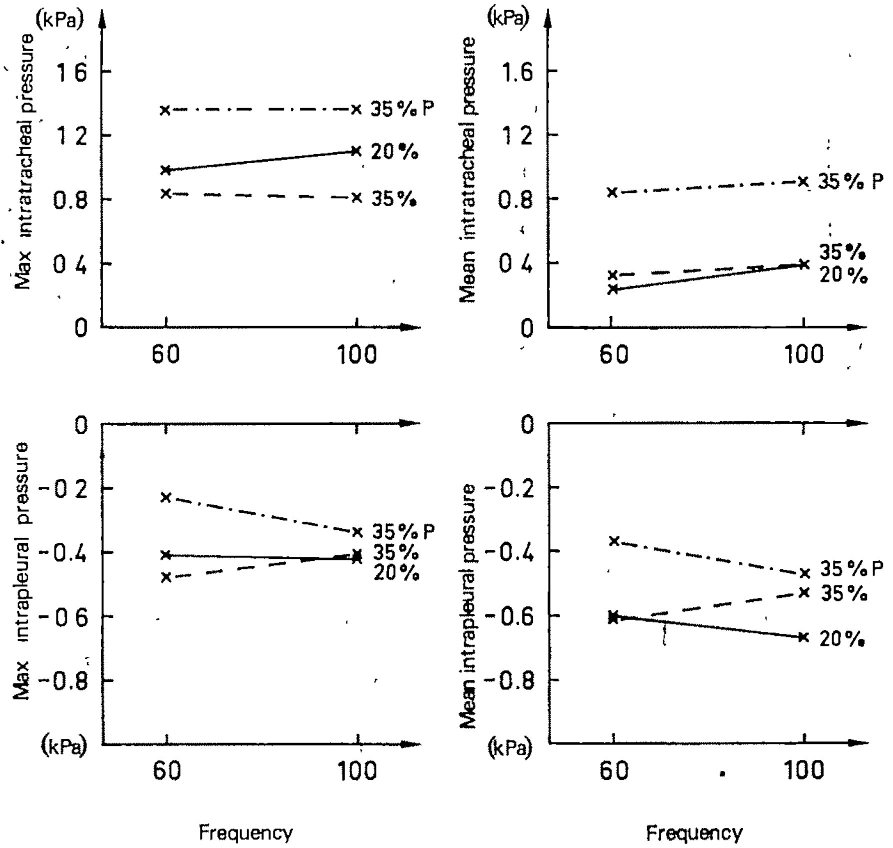


FIG. 3. Maximum and mean intratracheal and intrapleural pressures in relation to ventilatory frequency (b.p.m.) and insufflation period (per cent of the ventilatory cycle) (P = ventilation with a positive end-expiratory pressure of 0.5 kPa).

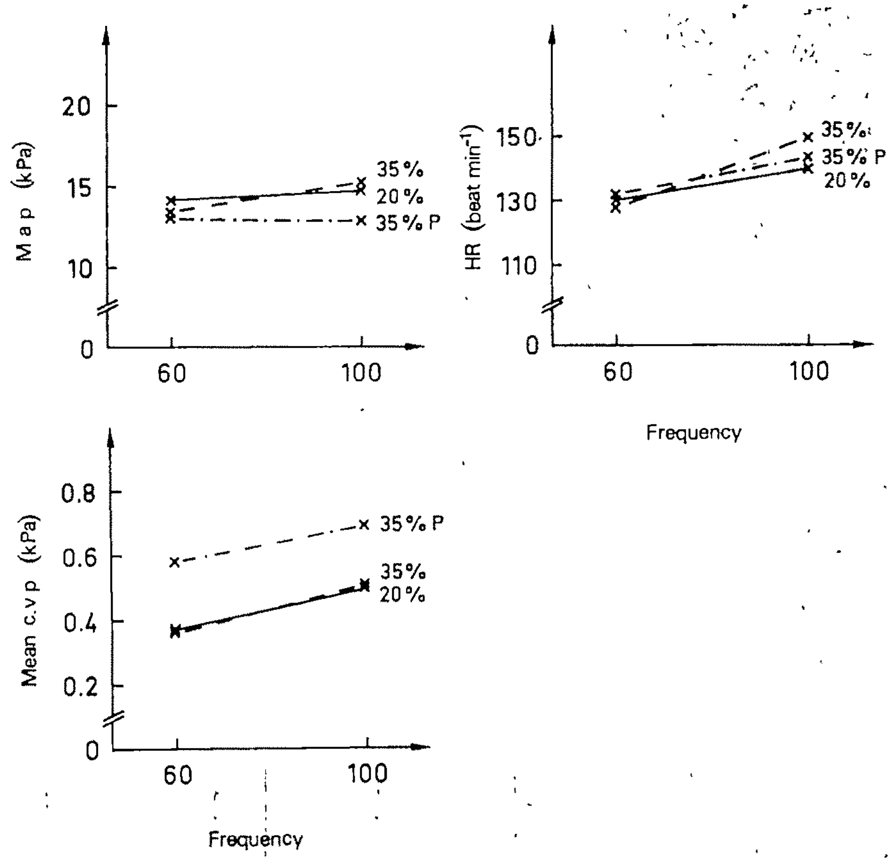


FIG. 4. Mean arterial pressure (m.a.p.), central venous pressure (c.v.p.) and heart rate (HR) in relation to ventilatory frequency (P = ventilation with a positive end-expiratory pressure of 0.5 kPa).

central venous pressure. Faster heart rates were always noted at a ventilatory frequency of 100 b.p.m. The arterial pressure was about the same irrespective of the ventilation pattern.

DISCUSSION

A decrease in FRC and a concomitant increase in venous admixture in patients with no primary pulmonary disease are known to occur during anaesthesia and to some extent during intensive care. The mechanisms causing this reduction in FRC are still unexplained (Hewlett et al., 1974; Nunn, 1977). In neonatal pulmonary disorders, alveolar collapse and a reduction of FRC have serious consequences, since many of the regulatory mechanisms involved in the circulatory adaptation after birth depend on an adequate ventilation.

CPAP (Gregory et al., 1971) and PEEP (Ashbaugh et al., 1969) are widely used to balance decreased compliance and improve oxygenation. When the lung compliance is normal, CPAP and PEEP will prevent the completion of expiration and cause an increase in FRC (Nunn, 1977; see fig. 2). The influences of the ventilatory pattern on FRC are essentially unknown. A greater ventilatory frequency seems to offer advantages in its effects on circulation and compliance (Jonzon et al., 1971) and on FRC (Nisbet, Dobbinson and Steward, 1974). The ventilatory frequency range of 60–100 b.p.m. was chosen for this investigation.

The experiments were performed on cats in order to obtain ventilatory conditions comparable to those in infants. Anaesthesia was given with chloralose, which causes exaggerated reflex activity (Balis and Monroe, 1964). The influence of the muscular tone on the intrathoracic gas volume during the experiments could be considered constant.

Ventilation without PEEP

During ventilation at a frequency of 100 b.p.m. and an insufflation period of 20%, FRC 0.112 litre was obtained, which was 10% greater than that during spontaneous breathing (0.102 litre) under anaesthesia. FRC 0.112 litre would be close to the normal FRC (unanaesthetized) in the cat, since the reduction in FRC with anaesthesia (20% (Nunn, 1977)) is probably less when chloralose is used as the anaesthetic.

The administered minute ventilation per kg body weight was less than that used by Nisbet, Dobbinson and Steward (1974), but the alveolar ventilation was still adequate as judged from the blood-gases. With the short inspiratory period and the fast mean inspiratory flow rate (100 b.p.m., 20% insufflation; fig. 5), the pressure in the airway during insufflation was sufficient to overcome the resistance to flow and to expand the alveoli. This resulted in adequate ventilation at FRC close to that during spontaneous breathing and also in small intrapleural pressures (cf. fig. 4).

During ventilation at a frequency of 100 b.p.m. with a longer insufflation period and during ventilation at a slower frequency (60 b.p.m.), the inspiratory flow rates (fig. 5) were less and the distension of the lung more pronounced, as expressed by the pressure transmitted to the pleural space (see fig. 3), and FRC was greater. With lungs of normal compliance it is possible that the expiratory flow rates were too slow and expiration not fully completed, resulting in moderate expansion of the lung at the end of expiration and thus greater FRC. Studies on the relation between deadspace ventilation and ventilatory settings are in progress.

Ventilation with PEEP

A proportional and significant increase in FRC at both ventilatory frequencies was noted when 0.5 kPa PEEP was added. FRC values 23–27% greater than

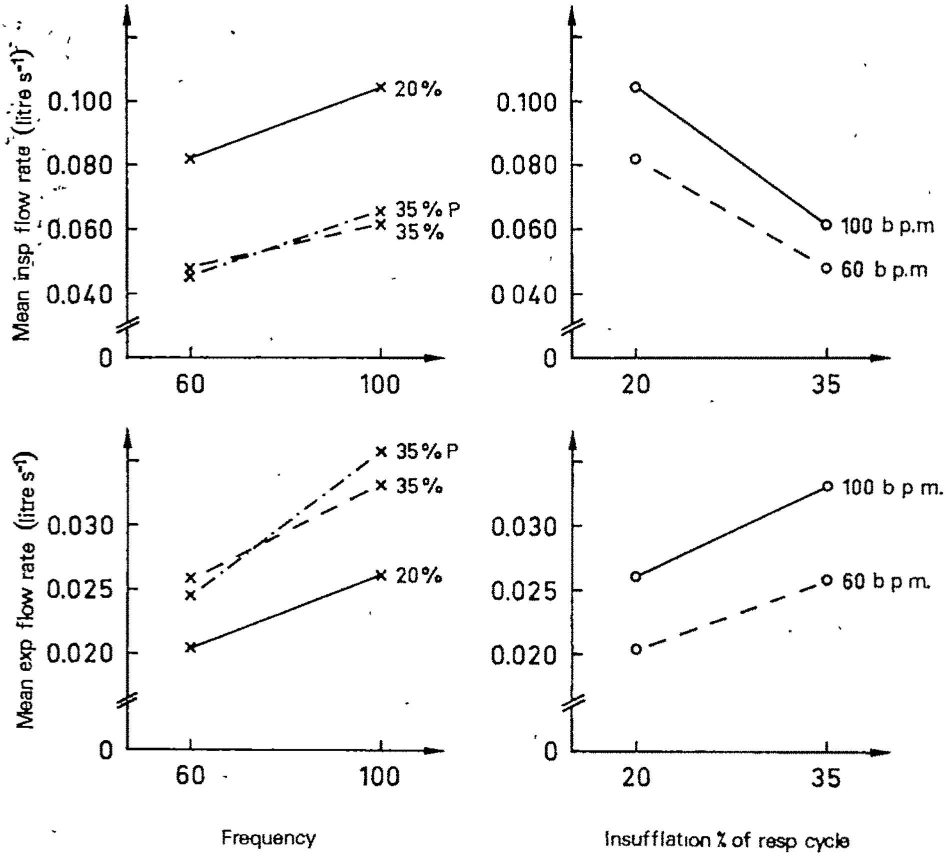


FIG. 5. Mean inspiratory and expiratory flow rate in relation to ventilatory frequency (b.p.m.) and insufflation period (per cent of the ventilatory cycle) (P = ventilation with a positive end-expiratory pressure of 0.5 kPa).

those during ventilation without PEEP were obtained. This is a slightly greater difference than that observed by McIntyre, Laws and Ramachandran (1969) who used the same PEEP in patients suffering from respiratory insufficiency.

There was no change in tidal volume when PEEP was added and no significant change in Pa_{CO_2}. Thus the increase in FRC with PEEP did not alter the alveolar ventilation although a greater part of the total lung volume was included in FRC. Since the lung had normal compliance, the pressure was transmitted to the pleural space with an increase in central venous pressure.

CONCLUSIONS

Under the conditions in which this study was performed, with almost the same alveolar ventilation at all ventilatory settings, it can be concluded that:

Ventilation at a fast frequency of 100 b.p.m. and with a short insufflation period (20% of the ventilatory cycle) could produce FRC of the same magnitude as that prevailing during spontaneous breathing.

Ventilation at a frequency of 60 b.p.m. resulted in a greater FRC than ventilation at a frequency of 100 b.p.m.

Ventilation with an insufflation period of 35% produced a greater FRC than when a shorter period of insufflation (20%) was used.

Adequate alveolar ventilation at a fast ventilatory frequency could be obtained at small intrapleural pressures.

Application of 0.5 kPa PEEP caused an increase in FRC of 23–27% during high-frequency positive-pressure ventilation.

ACKNOWLEDGEMENTS

This study was performed as a part of the scientific exchange programme between Poland and Sweden and was supported financially through the respective medical boards. Farum Industries, Warsaw, kindly placed a Relog Infant G-19 Respirator at our disposal and also provided expert technical assistance through Mr A. Weigl, to whom we are indebted. The authors wish to thank Mrs B. Östmark for skilful laboratory and technical assistance and E. Ekström, S. G. Nilsson, S. G. Norberg and O. Wistrand for expert technical assistance.

REFERENCES

Ashbaugh, D. G., Petty, T. L., Bigelow, D. B., and Harris, T. M. (1969). Continuous positive-airway pressure breathing (CPPB) in adult respiratory distress syndrome. *J. Thorac. Cardiovasc. Surg.*, **57**, 31.

Balis, G. V., and Monroe, R. R. (1964). The pharmacology of chloralose. *Psychopharmacologia*, **6**, 1.

Don, H. F., Wahba, W. M., and Craig, D. B. (1972). Airway closure, gas trapping, and the functional residual capacity during anesthesia. *Anesthesiology*, **36**, 533.

Eriksson, I., Jonzon, A., Sedin, G., and Sjöstrand, U. (1977). The influence of the ventilatory pattern on ventilation, circulation and oxygen transport during continuous positive-pressure ventilation. An experimental study. *Acta Anaesthesiol. Scand.* (Suppl.), **64**, 149.

Gregory, G. A., Kitterman, J. A., Phibbs, R. H., Tooley, W. H., and Hamilton, K. H. (1971). Treatment of idiopathic respiratory distress syndrome with continuous positive airway pressure. *N. Engl. J. Med.*, **284**, 1333.

Hewlett, A. M., Hulands, G. H., Nunn, J. F., and Heath, J. R. (1974). Functional residual capacity. II: Spontaneous respiration. *Br. J. Anaesth.*, **46**, 486.

Jonzon, A., Öberg, P. A., Sedin, G., and Sjöstrand, U. (1971). High-frequency positive-pressure ventilation by endotracheal insufflation. *Acta Anaesthesiol. Scand.* (Suppl.), **43**, 1.

—— Sedin, G., and Sjöstrand, U. (1973). High-frequency positive-pressure ventilation (HFPPV) applied for small lung ventilation and compared with spontaneous respiration and continuous positive airway pressure (CPAP). *Acta Anaesthesiol. Scand.* (Suppl.) **53**, 23.

McIntyre, R. W., Laws, A. K., and Ramachandran, P. R. (1969). Positive expiratory pressure plateau. Improved gas exchange during mechanical ventilation. *Can. Anaesth. Soc. J.*, **16**, 477.

Nisbet, H. I. A., Dobbinson, T. L., and Steward, D. J. (1974). The effect of artificial ventilation on FRC and arterial oxygenation. *Can. Anaesth. Soc. J.*, **21**, 215.

Nunn, J. F. (1977). *Applied Respiratory Physiology*, 2nd edn, p. 68. London, Boston: Butterworths.

Peters, R. M. (1969). *The Mechanical Basis of Respiration*, 1st edn, p. 45. London: J. & A. Churchill.

Prod'hom, L. S., Levison, H., Cherry, R. B., and Smith, C. A. (1965). Adjustment of ventilation, intrapulmonary gas exchange, and acid–base balance during the first day of life. Infants with early respiratory distress. *Pediatrics*, **35**, 662.

Rondio, Z. (1979). The choice of ventilator in Warsaw; in *Paediatric Anaesthesia—Ventilatory Assistance Following Neonatal Surgery*, Proc. Ann. Meeting Assoc. Paediatric Anaesthetists G.B. and Ireland, March 11, 1978. Abbot Laboratories Ltd, 1979.

—— Jonzon, A., and Sedin, G. (1978). Functional residual capacity (FRC) during high-frequency positive-pressure ventilation. *V. European Congress of Anaesthesiology*, Paris, September 4–9, 1978, Abstract 115. Excerpta Medica International Congress Series No. 452, 1978.

—— and Ryterski, S. (1978). Frequency dependent parameters in the assessment of the Relog-infant ventilator. *V. European Congress of Anaesthesiology*, Paris, September 4–9, 1978. Abstract 116. Excerpta Medica International Congress Series No. 452, 1978.

CAPACITE FONCTIONNELLE RESIDUELLE ET PRESSIONS VENTILATOIRES PENDANT UNE VENTILATION SOUS PRESSION POSITIVE A HAUTES FREQUENCES

RESUME

La capacité fonctionnelle résiduelle (FRC) a été mesurée sur des chats grâce à la technique d'extraction de l'azote par lavage pendant une ventilation sous pression positive. On a utilisé des fréquences de 60 et de 100 respirations/minute avec des périodes d'insufflation de 20% et de 35% du cycle ventilatoire, sans et avec pression positive en fin d'expiration. La fréquence plus haute combinée avec la période d'insufflation plus courte ont donné une FRC approchant de celle obtenue pendant la respiration spontanée. La fréquence plus basse et la période d'insufflation plus longue ont toujours donné de plus fortes valeurs de FRC. On a obtenu une augmentation supplémentaire de la FRC, de l'ordre de 23–27%, après application d'une pression positive de 0,5 kPa en fin d'expiration. On est arrivé à avoir une ventilation adéquate avec de faibles pressions intra-trachéales et intrapleurales à tous les réglages utilisés.

FUNKTIONELLE RESTKAPAZITÄT UND VENTILATORISCHER DRUCK BEI POSITIVER DRUCKBELÜFTUNG MIT HOHEN FREQUENZEN

ZUSAMMENFASSUNG

Die funktionelle Restkapazität (FRC) wurde bei Katzen mittels der Stickstoff-Ausspülmethode während positiver Druckbelüftung gemessen. Frequenzen von 60 und 100 b.p.m. wurden bei 20% und 35% des Belüftungszyklus' verwendet, ohne und mit positiven Endausatmungsdruck. Die höhere Frequenz zusammen mit der kürzeren Insufflationsperiode ergab eine FRC ganz wie bei spontaner Atmung. Die niedrigere Frequenz zusammen mit der längeren Insufflationsperiode ergab stets grössere FRC-Werte. Ein weiterer FRC-Anstieg von etwa 23–27% wurde bei Anwendung eines positiven Endausatmungsdruckes von 0,5 kPa erzielt. Eine ausreichende Belüftung wurde mit niedrigen intratrachealen und intrapleuralen Drucken bei allen verwendeten Einstellungen erzielt.

CAPACIDAD RESIDUAL FUNCIONAL Y PRESIONES VENTILATORIAS DURANTE VENTILACION POR PRESION POSITIVA EN ALTAS FRECUENCIAS

SUMARIO

Se midió la capacidad residual funcional (CRF) en gatos mediante la técnica de lavado por nitrógeno durante la ventilación por presión positiva. Se usó frecuencias de 60 y 100 b.p.m. con períodos de insuflación del 20 y del 35% del ciclo ventilatorio, con y sin presión expiratoria terminal positiva. La mayor frecuencia combinada con el periodo de insuflación más corto tuvo como resultado una CRF más cercana a la obtenida durante la respiración espontánea. Una frecuencia más baja y un periodo de insuflación más largo siempre tuvieron por efecto valores mayores de la CRF. Se obtuvo un aumento adicional de la CRF de cerca del 23–27% después de la aplicación de una presión expiratoria terminal positiva de 0,5 kPa. Se consiguió una ventilación adecuada por medio de presiones intratraqueales e intrapleurales pequeñas en todas las graduaciones utilizadas.

Br. J. Anaesth. (1980), **52**, 403

ARTERY-TO-MUSCLE ONSET TIME FOR NEUROMUSCULAR BLOCKING DRUGS

B. MINSAAS AND J. STOVNER

SUMMARY

Artery-to-muscle (A–M) onset time for five neuromuscular blocking agents was studied in 50 female patients under light endotracheal anaesthesia. Circulation to the right arm was occluded by a tourniquet and released 1 min after the injection i.v. into the left arm of a myoneural blocking drug. Muscle twitches were recorded in the right hand after stimulation of the ulnar nerve (1 Hz). After releasing the tourniquet the response to single twitches continued without decrease in height (latent onset time). The onset of gradual decreases in twitch height was noted, and the time until 90% depression of twitch height was measured (manifest onset time). The mean latent onset times were: pancuronium 31.9 s, tubocurarine 21 s, alcuronium 17.2 s, fazadinium 8.6 s and suxamethonium 4.8 s. Mean A–M latent onset time was significantly different for each drug ($P < 0.005$). Manifest A–M onset times were related to A–M latent onset times except for tubocurarine which exhibited a slower decline in twitch height. A–M latent onset time correlated well with the values for intravenous onset times reported in the literature.

The present study was undertaken to investigate the suitability of a method for the evaluation of the speed of onset of neuromuscular blocking drugs. Previously, such studies have been undertaken by measuring the time from the i.v. injection of the drug to the depression of the muscle twitch or the adequacy of tracheal intubation conditions. However, venous-arterial circulation time is variable (Harrison and Junius, 1972) and any evaluation of intubation conditions will always be subjective. The present method, proposed originally by Holst-Larsen (1976), eliminates inaccuracies as a result of the site and speed of injection and the venous–arterial circulation time. The neuromuscular blockers studied were pancuronium, tubocurarine, alcuronium, fazadinium and suxamethonium administered in doses used commonly for tracheal intubation.

PATIENTS AND METHODS

Fifty female patients were included in an open comparative study. Their ages varied between 28 and 50 yr and their weights from 49 to 75 kg. They were divided into five groups, one for each drug. The mean age and mean weight in each group and the mean drug doses are shown in table I. All patients were in good general health and about to undergo gynaecological operations for non-malignant conditions. Patients with cardiac, neurological or skeletal diseases were excluded. The patients were premedicated with pethidine 50–75 mg and atropine 0.6 mg. An indwelling catheter was inserted to a vein, usually on the back of the *left* hand, and connected to a continuous infusion of a Ringer acetate solution. Anaesthesia was induced with diazepam 5–10 mg i.v. followed by thiopentone 200–450 mg (mean dose 260 mg).

TABLE I. *Mean age, weight and drug dose in the five groups of patients*

Drug group	Mean age (yr)	Mean weight (kg)	*n*	Mean dose (mg kg^{-1})
Pancuronium	28.7	55.6	10	0.1
Tubocurarine	36.3	57.6	10	0.5
Alcuronium	41.3	59.2	10	0.3
Fazadinium	31.7	56.6	10	1.0
Suxamethonium	34.4	56.6	10	1.0

Between 2 and 3 min after the injection of thiopentone and with the eyelash reflex abolished, a tourniquet on the *right* arm was inflated beyond 200 mm Hg and the appropriate dose of neuromuscular blocking drug injected. Neuromuscular blocking drugs were administered via the *left* hand, randomly in the doses shown in table I. The ulnar nerve of the right arm was stimulated with a Block-Aid nerve stimulator (Burroughs Wellcome & Co., 1976), using skin surface electrodes. Maximum

---

BØRGE MINSAAS,* M.D.; JACOB STOVNER, F.F.A.R.C.S.; Department of Anaesthesia, The University Hospital, Rikshospitalet, Oslo 1, Norway.

* Present address: Norwegian Petroleum Directorate, Box 600, 4001 Stavanger, Norway.

0007-0912/80/040403-05 $01.00

© Macmillan Journals Ltd 1980

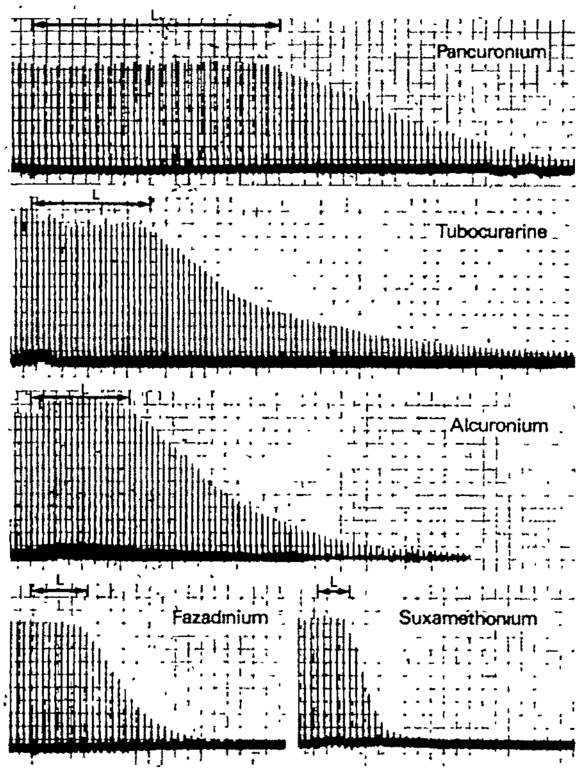


FIG. 1. Recording strips for the five drugs arranged according to the duration of A–M latent onset time. This period is marked L.

TABLE II. *Mean artery-to-muscle (A–M) onset times for the five drugs with SEM and SD. P values for significance of differences between drugs are shown (t test). PANC = pancuronium; TUB = tubocurarine; ALC = alcuronium; FAZ = fazadinium; SUX = suxamethonium*

	PANC	TUB	ALC	FAZ	SUX
LATENT A–M onset time (s)					
Mean	31.9	21.0	17.2	8.6	4.8
SEM	±2.87	±1.26	±0.62	±0.38	±0.24
SD	±6.41	±4.00	±1.95	±1.20	±0.75
P		<0.0005	<0.005	<0.0005	<0.0005
MANIFEST A–M onset time (s)					
Mean	32.8	41.1	25.0	11.7	5.8
SEM	±1.79	±3.60	±2.84	±0.81	±0.56
SD	±5.65	±11.37	±8.99	±2.56	±1.77
P		<0.025	<0.005	<0.0005	<0.0005
TOTAL A–M onset time (s)					
Mean	64.7	61.1	42.2	20.3	10.6
SEM	±2.72	±3.60	±2.62	±1.08	±0.46
SD	±8.61	±11.40	±8.30	±3.41	±1.02
P		n.s.	<0.0005	<0.0025	<0.0005

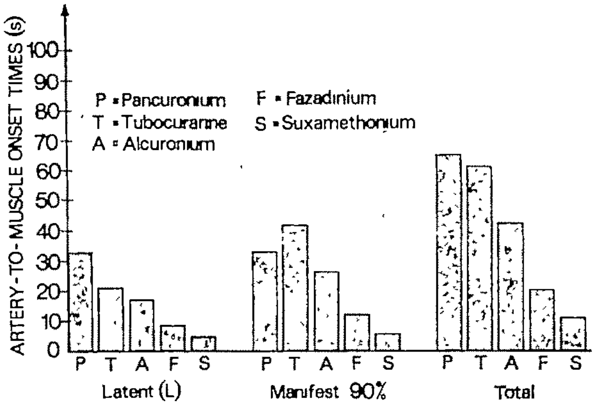


FIG. 2. Mean A–M onset times. Except for tubocurarine a long A–M latent onset time is followed by a long manifest onset time and *vice versa*.

twitch responses were obtained with the stimulator setting at step 6 or 8, after which the setting was increased to 10 to make sure that the stimulus was supramaximal. Muscle twitches (movement of a pneumatic bulb held in the right hand) were recorded on a Mingograph recorder (Elema–Schønander EMT 34 transducer). Paper speed was 2.5 mm s^{-1} and the ulnar nerve was stimulated at 1 Hz. One minute after the end of the rapid injection of the neuromuscular blocker in the *left* arm, the tourniquet on the *right* arm was released suddenly. Twitches were recorded until the block was complete and at 90% decrease in twitch height the time was noted and endotracheal intubation performed immediately.

RESULTS

Following the sudden release of the cuff pressure (time noted) single twitches continued for a period without alteration in twitch height. This was followed by a clearly defined change showing a gradual decrease in twitch height (fig. 1). The time from the release of the cuff pressure until the first change in twitch height was called the A–M latent onset time (line L in fig. 1). The period from the first evidence of any decrease in twitch height until 90% depression of twitch height was called the A–M manifest onset time. The A–M latent onset time plus the A–M manifest onset time equals the A–M total onset time (table II).

It can be seen that there were significant differences between the drugs studied with regard to A–M latent onset times and A–M manifest onset times

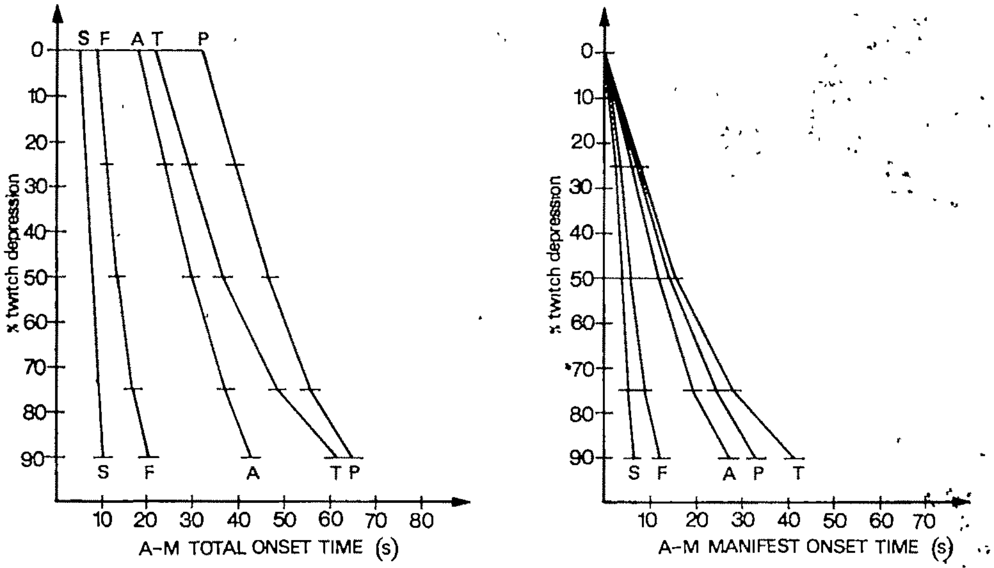


FIG. 3. The different onset times for each drug indicated by per cent depression of twitch height. S = suxamethonium, F = fazadinium, A = alcuronium, T = tubocurarine, P = pancuronium. The horizontal line at 0% in the first graph indicates A-M latent onset times.

although it will be observed that, whereas pancuronium had a longer A-M latent onset time than tubocurarine, it had a shorter A-M manifest onset time (table II). The opposite was true for tubocurarine which had a comparatively rapid A-M latent onset time and a slow and variable A-M manifest onset time. Thus, there was no significant difference in the A-M total onset time between these two drugs.

DISCUSSION

Since, in clinical practice, neuromuscular blocking agents are injected i.v., the time from the i.v. injection of the drug to full neuromuscular blockade is of importance. This period is made up, to a large extent, by the circulation time, which involves possible delays in the right heart, the lungs, the left heart and the vessels. Harrison and Junius (1972) showed that vein-to-artery circulation time was more than doubled in patients with circulatory failure. This variable was eliminated in our study by measuring the time from the release of the tourniquet to the various alterations in twitch height. By this method we found an A-M latent onset time unique for each drug, a feature which has not been described previously following the administration i.v. of alcuronium tubocuronium or pancuronium (Harrison, 1972; Hey, 1973; Blackburn and Morgan, 1978).

One minute was chosen as the most appropriate period of occlusion of the circulation to the one arm after the injection i.v. of the drug; this was considered to be the minimum time necessary to allow even distribution of the injected drug in the circulation (Kalow, 1959). Thus on release of the tourniquet, "bolus" effects would be avoided.

The i.v. onset time should equal the A-M latent onset time plus the 30 s found as an average vein-to-artery circulation time by Harrison and Junius (1972). Blackburn and Morgan (1978) have determined, in patients with normal circulations, the times from the i.v. administration of a drug until the production of a 25% depression of twitch height with four of the neuromuscular blockers we have used. With these four drugs our A-M latent onset times plus 30 s came within 10% of the i.v. onset times found by Blackburn and Morgan (1978). This shows that artery-to-muscle latent onset time is a valid indicator of the speed of onset of a neuromuscular blocker.

A-M latent onset time must represent the time for the relaxant to (a) gain access to the receptors; (b) occupy the receptors sufficiently for blockade to occur. So far we can only speculate on the role played by each of these processes. For suxamethonium, however, we must presume that the value (4.8 s) found for this drug represented access time only, because the drug is principally an agonist acting instantaneously with the receptors. The 4.8 s found in our study is extremely close to the 4 s onset time found for acetylcholine itself after injection to the brachial artery in humans (Grob, Johns and Harvey, 1956).

If the artery-to-muscle latent onset time represents mainly access to the receptors by diffusion, certain physicochemical factors should be of importance. No correlation, however, could be found between latent onset time and the square root of the molecular weight, although this last factor is thought to determine speed of diffusion along a concentration gradient. Information on protein binding is available only for suxamethonium, pancuronium and tubocurarine (Cohen, Brewer and Smith, 1967;) Dal Santo, 1968; Thompson, 1976). Of these drugs the last two are protein bound and have the longest onset times while the first is free and has the shortest onset time.

Receptor occupancy by non-depolarizing drugs was shown by Waud and Waud (1975) to have a safety margin of 75–90% for the transmission of single twitches. Paton (1961), in his kinetic theory, proposed that the speed of action of neuromuscular blockers reflected their rate of receptor occupancy. In 1967, however, Waud applied neuromuscular blocking drugs directly to the receptors in animals and found that they acted as if access was the only rate-limiting factor. In a later review (Waud, 1968), however, he admits that the rate of combination with the receptor provides a satisfactory explanation for the speed of onset of drugs. This explains why the speed of onset is inversely related to potency. This postulate agrees only partly with our results. Pancuronium, the most potent myoneural blocking drug on the market, has the longest A–M latent onset time. Alcuronium, on the other hand, is more potent than tubocurarine but has a shorter A–M latent onset time and does not fit into the postulate.

In 1973 Feldman showed that depolarizers, such as suxamethonium, lost their effect on the human hand muscles in 1–2 min compared with 15–20 min for the non-depolarizers. It is possible that the non-depolarizers have a stronger affinity for the receptors which manifests itself as a slow onset and a slow dissociation rate whereas the opposite is the case for depolarizers.

REFERENCES

Blackburn, C. L., and Morgan, M. (1978). Comparison of speed of onset of fazadinium, pancuronium, tubocurarine and suxamethonium. *Br. J. Anaesth.*, **50**, 361.

Cohen, N., Brewer, H. W., and Smith, D. (1967). Metabolism and elimination of d-tubocurarine-H^3. *Anesthesiology*, **28**, 311.

Dal Santo, G. (1968). Kinetics of distribution of radioactive labelled muscle relaxants. *Anesthesiology*, **29**, 435.

Feldman, S. A. (1973). *Muscle Relaxants* (ed. S. A. Feldman), p. 65. London: W. B. Saunders.

Grob, D., Johns, R. J., and Harvey, A. M. (1956). Studies in neuromuscular function. *Bull. Johns Hopkins Hosp.*, **99**, 136.

Harrison, G. A. (1972). The cardiovascular effects and some relaxant properties of four relaxants in patients about to undergo cardiac surgery. *Br. J. Anaesth.*, **44**, 485.

—— Junius, F. (1972). The effect of circulation time on the neuromuscular action of suxamethonium. *Anaesth. Intens. Care*, **1**, 33.

Hey, V. F. M. (1973). Relaxants for endotracheal intubation. *Anaesthesia*, **28**, 32.

Holst-Larsen, H. (1976). The hydrolysis of suxamethonium in human blood. *Br. J. Anaesth.*, **48**, 887.

Kalow, W. (1959). The distribution, destruction and elimination of muscle relaxants. *Anesthesiology*, **20**, 505.

Paton, W. D. M. (1961). A theory of drug action based on the rate of drug receptor combination. *Proc. R. Soc. B.*, **154**, 21.

Thompson, J. M. (1976). Pancuronium binding by serum proteins. *Anaesthesia*, **31**, 219.

Waud, B. E., and Waud, D. R. (1975). Physiology and pharmacology of neuromuscular blocking agents; in *Muscle Relaxants* (ed. R. L. Katz), p.1. Amsterdam: Excerpta Medica.

Waud, D. R. (1967). The rate of action of competitive neuromuscular blocking agents. *J. Pharmacol. Exp. Ther.*, **158**, 99.

—— (1968). Pharmacological receptors. *Pharmacol. Rev.*, **20**, 49.

PERIODE D'INVASION ARTERE-MUSCLE DE CINQ AGENTS DE BLOCAGE NEUROMUSCULAIRE

RESUME

La période d'invasion artère-muscle (A–M) de cinq agents de blocage neuromusculaire a été étudiée sur cinquante femmes subissant une intervention sous anesthésie endotrachéale légère. La circulation du bras droit a été arrêtée par un tourniquet, puis relâchée une minute après l'injection intraveineuse d'un agent de blocage musculo-nerveux dans le bras gauche. Des contractions du muscle ont été enregistrées dans la main droite après stimulation du nerf ulnaire (1 Hz). Après avoir relâché le tourniquet, la réaction aux contractions isolées s'est poursuivie sans diminution de l'intensité (départ de réaction latent). On a noté le début des diminutions graduelles de l'intensité des contractions et on a chronométré le temps nécessaire pour atteindre 90% de la diminution de l'intensité des contractions (départ manifeste de la réaction). Les temps latents moyens nécessaires au départ de la réaction ont été les suivants: pancuronium 31,9 s, tubocurarine 21 s, alcuronium 17,2 s, fazadinium 8,6 s et suxaméthonium 4,8 s. Le temps latent moyen nécessaire au départ de la réaction A–M a été nettement différent pour chaque agent ($P < 0,005$). Les

temps de manifestation nécessaires au départ de la réaction A–M ont été reliés aux temps latents moyens nécessaires au départ de la réaction A–M sauf pour la tubocurarine, qui a accusé une baisse plus lente dans l'intensité de la contraction. Les temps latents nécessaires au départ de la réaction A–M ont été en bonne corrélation avec les valeurs des périodes d'invasion intraveineuse signalées dans la documentation.

ARTERIE-BIS-MUSKEL-WIRKUNGSEINTRITTSZEIT BEI NEUROMUSKULÄREN BLOCKIERUNGSDROGEN

ZUSAMMENFASSUNG

Die Arterie-bis-Muskel-Wirkungseintrittszeit bei fünf neuromuskulären Blockierungsdrogen wurde bei 50 Patientinnen unter leichter endotrachealer Anasthesie studiert. Die Zirkulation zum rechten Arm wurde durch einen Knebel unterbunden, der 1 min nach der Injektion intravenös in den linken Arm einer myoneuralen Blockierungsdroge gelöst wurde. Die Muskelzuckungen in der rechten Hand wurden nach Stimulierung (1 Hz) des Ulnarnervs aufgezeichnet. Nach Lösung des Knebels ging die Reaktion auf Einzelzuckungen ohne Verminderung an Höhe (latente Eintrittszeit) weiter. Der Eintritt gradueller Verminderungen der Zuckungshöhe wurde festgestellt, und die Dauer bis zur 90%igen Unterdrückung der Zuckhöhe (offensichtliche Eintrittszeit) wurde gemessen. Die mittleren latenten Eintrittszeiten waren: Pancuronium 31,9 s, Tubocurarin 21 s, Alcuronium 17,2 s, Fazadinium 8,6 s und Suxamethonium 4,8 s. Die mittlere Arterie-bis-Muskel-Wirkungseintrittszeit (latent) war für jede Droge deutlich verschieden ($P<0,005$). Die offensichtlichen A–M-Wirkungseintrittszeiten waren auf die latente A–M-Wirkungseintrittszeit abgestimmt, ausser bei Tubocurarin, das einen langsameren Abstieg der Zuckhöhe zeigte. Die latente A–M-Wirkungseintrittszeit war gut auf die Werte für intravenose Eintrittszeiten abgestimmt, wie sie in der Literatur zu finden sind.

PRINCIPIO DEL EFECTO ARTERIA-A-MUSCULO DE SUBSTANCIAS DE BLOQUEO NEUROMUSCULAR

SUMMARIO

Se llevó a cabo un estudio del principio del efecto arteria-a-músculo (AM) de cinco agentes bloqueadores neuromusculares en 50 pacientes femininas bajo anestesia endotraqueal ligera. Se obstruyó la circulación en el brazo derecho mediante un torquinete y se soltó 1 min después de la inyección i.v. en el brazo izquierdo de una substancia bloqueadora mioneural. Se registraron los crispamientos espasmódicos musculares en la mano derecha después de estimular al nervio ulnar (1 Hz). Una vez soltado el torquinete, la respuesta a crispamientos únicos siguió sin disminuir en su altura (tiempo de iniciación latente). Se observó la iniciación de disminuciones progresivas de la altura del crispamiento y se midió el tiempo hasta que la altura hubiera bajado en un 90% (tiempo de iniciación manifiesto). Los tiempos medios de iniciación latente fueron: pancuronio (31,9 s), tubocurarina (21 s), alcuronio (17,2 s), fazadinio (8,6 s) et suxametonio 4,8 s). El tiempo de iniciación latente promedio (AM) difirió significativamente para cada droga ($P<0,005$). Los timepos de iniciación manifiestos (AM) se relacionaban a los tiempos de iniciación latente (AM), salvo en el caso de la tubocurarina que demostró un descenso más lento de la altura del crispamiento. El tiempo de iniciación latente (AM) se correlacionaba bien con los valores de los tiempos de iniciación intravenosos indicados en la folletería.

Br. J. Anaesth. (1980), **52**, 409

SUPRACLAVICULAR BRACHIAL PLEXUS BLOCK USING A NERVE STIMULATOR AND AN INSULATED NEEDLE

I. YASUDA, T. HIRANO, T. OJIMA, N. OHHIRA, T. KANEKO AND M. YAMAMURO

SUMMARY

A technique employing a nerve stimulator and an insulated needle was used for supraclavicular brachial plexus block in 71 patients using 0.5% plain bupivacaine 15–20 ml. The mean minimal stimulating current to produce paraesthesia was 0.09 mA. The plexus was identified at a mean depth of 27 mm below the skin. The block was successful in 98% of patients when the stimulation was felt in the index, middle or ring finger, but was often incomplete when felt in the thumb or little finger.

The use of a portable nerve stimulator increases the success of regional nerve blocks (Greenblatt and Denson, 1962; Koons, 1969; Wright, 1969), and provides a precise, safe method of identifying the brachial plexus by the supraclavicular route. Using this technique we decided to study the minimum stimulating current required, the depth of the plexus beneath the skin and the relationship of the completeness of blockade to the distribution of paraesthesia elicited following insertion of the needle.

METHODS

Seventy-one patients undergoing operative procedures (table I) on the upper limb were studied. A ground electrode (an electrocardiograph plate) was attached to the opposite limb, and connected to the output pole of a Digital (M.E.C., M.E.–6211) stimulator. A 23-gauge insulated needle (Pole injector), 50 mm long, was connected to the other pole with an alligator clamp (fig. 1).

TABLE I. *Operative procedures in 71 blocks*

Operative procedures	No. of patients
Open reduction of fracture, or osteotomy	17
Sinovectomy	14
Tenolysis and tendon suture	12
Removal of the plate	8
Wound toilet and suture	7
Replantation of severed fingers	4
Neurolysis	4
Curettage	3
Open reduction of dislocation	2

A marker was placed 3 cm from the tip of the needle and the plexus was located using the supraclavicular approach (Moore, 1976). When paraesthesia or shock-like sensations were elicited, the distribution was noted, the needle was fixed and the depth of the tip from the skin was measured. The stimulating current (initially 0.2 mA for 5 ms at 1 Hz) was then decreased to determine the minimum current which would produce paraesthesia. If this current was less than 0.15 mA, 0.5% plain bupivacaine 15–20 ml was injected.

RESULTS

The minimal stimulating current required was 0.09 ± 0.007 mA (mean ± SEM) and the plexus depth was 27.1 ± 0.8 mm. The procedure took 13 ± 1 min and operative analgesia was established in 21 ± 1 min after injection. The operative procedures lasted between 35 min and 10 h 25 min. In two patients undergoing surgery for severed fingers, the blockade following a single injection was inadequate.

Table II shows the distribution of paraesthesiae in relation to the success of the local anaesthetic injection. Successful blocks to both radial and ulnar sides of the hand and the forearm were produced in 98% of patients experiencing paraesthesia of index, middle or ring fingers. The success rate was low when paraesthesia was felt in the thumb or little finger. Usually paraesthesia of the thumb led to unsuccessful analgesia of the little finger and *vice versa*.

ISAMU YASUDA, M.D., TOSHIO HIRANO, M.D.; Department of Anaesthesia, Tohoku Rosai Hospital, 3–21, Dainohara 4-chome, Sendai City, Miyagi Ken, 980, Japan. TADASHI OJIMA, M.D., NOBUHIRO OHHIRA, M.D.; Department of Orthopaedic Surgery, Tohoku Rosai Hospital. TADANOBU KANEKO, M.D.; MAKOTO YAMAMURO, M.D.; Department of Anaesthesiology, Tohoku University School of Medicine, Sendai, Japan.

0007–0912/80/040409–03 $01.00

© Macmillan Journals Ltd 1980

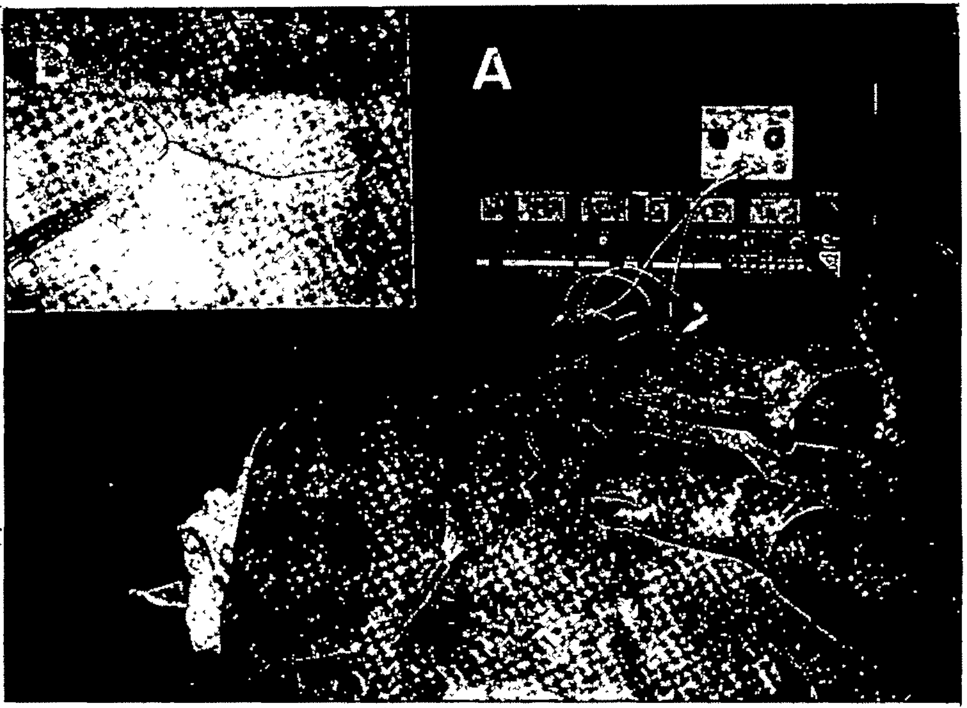


FIG. 1. To show the nerve stimulator and insulated needle, with marker, used in this study.

TABLE II. *Relationship between distribution of paraesthesia and successful blockade*

Distribution of paraesthesiae	No. of successful blocks	No. of unsuccessful blocks
Thumb	0	3
Index finger	12	0
Middle finger	35	1
Ring finger	4	0
Little finger	7	3
Hand	2	1
Elbow	2	1
Total	62	9

Since there are no other published data on the minimal current required when a nerve stimulator is used to identify the correct point of injection in brachial plexus block, we determined the mean minimal current required to produce muscle twitch of the fingers by direct stimulation of the plexus in five patients undergoing radical mastectomy. Under halothane anaesthesia the minimal current was 0.12±0.004 mA. The stimulating current in our conscious patients was 0.09±0.007 mA and this indicates that our injections were made very close to the plexus.

DISCUSSION

Normally, two techniques are employed to ensure completeness of brachial plexus block. A larger volume of local anaesthetic may be injected, as recommended by Winnie (1970) using the interscalene approach. For supraclavicular block, Moore (1976) states that paraesthesia of all digits should be obtained and separate injections made for each. Our results suggest that both these may be unnecessary if paraesthesia of the middle three digits is obtained.

Pneumothorax is a major complication of the supraclavicular technique. Using our technique we found that patients described a knife-like pain, or electric sensation, in the lateral chest wall, or breathing difficulties when the needle approached the pleura, as has been reported by Wright (1969). Our findings of the depth of the plexus should be a warning against inserting the needle much more than 3 cm below the skin, a further safeguard. No pneumothorax or evidence of neural damage occurred in this series.

ACKNOWLEDGEMENT

The authors wish to express their thanks to Dr J. A. W. Wildsmith for his editorial assistance.

REFERENCES

Greenblatt, G. M., and Denson, J. S. (1962). Needle nerve stimulator-locator: nerve blocks with a new instrument for locating nerves. *Anesth. Analg.* (*Cleve.*), **41**, 599.

Koons, R. A. (1969). The use of the Block-Aid monitor and plastic intravenous cannulas for nerve blocks. *Anesthesiology*, **31**, 290.

Moore, D. C. (1976). *Regional Block*, 4th edn, p. 221. Springfield, Illinois: Charles C. Thomas.

Winnie, A. P. (1970). Interscalene brachial plexus block. *Anesth. Analg.* (*Cleve.*), **49**, 455.

Wright, B. D. (1969). A new use for the Block-Aid monitor. *Anesthesiology*, **30**, 236.

BLOCAGE DU PLEXUS BRACHIAL SUPRACLAVICULAIRE A L'AIDE D'UN STIMULATEUR DE NERF ET D'UNE AIGUILLE ISOLEE

RESUME

On a appliqué une technique basée sur un stimulateur de nerf et une aiguille isolée pour bloquer le plexus brachial supraclaviculaire de 71 patients, à l'aide de 15–20 ml de bupivacaine pure à 0,5%. Le courant de stimulation minimal moyen pour produire une paraesthésie a été de 0,09 m ampère. Le plexus a été identifié à une profondeur moyenne de 27 mm au-dessous de la peau. Le blocage a été satisfaisant dans 98% des cas, lorsque la stimulation a été ressentie dans l'index, le majeur ou l'annulaire, mais il a été souvent incomplet lorsque la stimulation a été ressentie dans le pouce ou l'auriculaire.

SUPRAKLAVIKULARE BRACHIALPLEXUS-BLOCKIERUNG MITTELS NERVENREIZMITTEL UND EINER INSULIERTEN NADEL

ZUSAMMENFASSUNG

Eine Methode unter Verwendung eines Nervenreizmittels und einer insulierten Nadel wurde bei 71 Patienten für eine supraklavikulare Brachiaplexus-Blockierung durch 0,5% reines Bupivacain 15–20 ml verwendet. Der mittlere Wert eines minimalen stimulierenden Stroms zur Hervorrufung von Parästhesie betrug 0,09 m amp. Der Plexus wurde in einer mittleren Tiefe von 27 mm unter der Haut identifiziert. Die Blockierung war bei 98% der Patienten erfolgreich, wenn der Reiz im Zeige-, Mittel- oder Ringfinger spürbar war, war aber oft unvollständig, wenn der Reiz im Daumen oder im kleinen Finger spürbar war.

BLOQUEO DEL PLEXO BRAQUIAL SUPRACLAVICULAR AL USAR UN ESTIMULADOR DE NERVIOS Y UNA AGUJA AISLADA

SUMMARIO

Se usó una técnica en base a un estimulador de nervios y una aguja aislada para el bloqueo braquial supraclavicular en 71 pacientes, administrándoles 15–20 ml de bupivacaina normal al 0,5%. La corriente estimuladora mínima media requerida para producir la parestesia era de 0,09 m amp. Se identificó el plexo a una profundidad media de 27 mm por debajo de la piel. Fue exitoso el bloqueo en el 98% de los pacientes cuando sentían la estimulación en el índice, el dedo cordial o el anular, pero fue a menudo incompleto cuando la sentían en el pulgar o el dedo meñique.

Br. J. Anaesth. (1980), **52**, 413

NEW ANAESTHETIC FORMULATION FOR EPICUTANEOUS APPLICATION TESTED FOR CUTTING SPLIT SKIN GRAFTS

L. OHLSÉN AND S. ENGLESSON

SUMMARY

Ane-Pad (A 2358, Astra Läkemedel AB), a new local anaesthetic formulation for application to the skin has been tested in the removal of split skin grafts. Ane-Pad is a thin cotton pad, containing a solution of 10% ketocaine base in a solvent mixture of isopropanol, glycerol and water. The pad has been used on the donor sites of 173 patients with a minimum application time of 1 h before surgery. Eighteen patients complained of slight, transient irritation immediately after application. After removal of the pad erythema was present in 39 patients and oedema in eight. In 157 patients (90.8%) analgesia was adequate. Two patients (1.1%) needed additional anaesthesia. The concentration of ketocaine in the blood was measured in 101 patients and did not exceed 850 ng ml^{-1}. There were no systemic side-effects.

The cutting of split skin grafts in plastic surgery is often the most painful part of the operation, especially when the recipient site does not require excision or suturing.

It has been difficult to achieve anaesthesia of intact skin by epicutaneous application as the skin offers an almost complete barrier to diffusion. Aprotic solvents, such as dimethyl sulphoxide (DMSO) might be a suitable enhancer for a local anaesthetic drug but it is liable to produce undesirable effects (Kligman, 1965; Brechner, Cohen and Pretsky, 1967; Rubin, 1975). Monash (1957) described the use of alcoholic solvents for topical anaesthesia and in 1971, Adriani and Dalili showed that the available local anaesthetics tested did not penetrate sufficiently to produce anaesthesia after topical application on unbroken skin. Although some of the formulations tested by these authors were effective for a short time or under certain conditions (Dalili and Adriani, 1971), they were not effective enough to warrant clinical testing.

A mixture of isopropanol, glycerol and water in proportions which achieve a saturated solution has, in animal experiments, been found to be as effective as aprotic solvent mixtures (Åkerman, 1978). Epicutaneous application of certain compositions containing ketocaine produced very effective anaesthesia (Åkerman, 1978). Ketocaine (fig. 1) is a potent local anaesthetic agent, being particularly active with regard to surface anaesthesia and after infiltration (Piccolo, 1964; Appiani and Laveneziana, 1966).

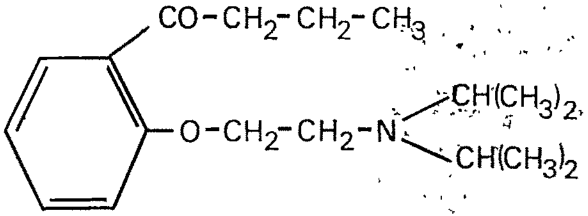


FIG. 1. The chemical structure of ketocaine. The basic pharmacology of ketocaine, 2'-(2-diisopropylaminoethoxy)-butyrophenone which belongs to the group of amino-ethers, was reported by Setnikar in 1966.

Ketocaine (Recordati, S.P.A., Milan, Italy) is very lipid-soluble, the partition coefficient between cod liver oil and water being approximately 8000 for ketocaine as compared with about 36 for lignocaine (Åkerman, in preparation). A second property that may facilitate the uptake of ketocaine is the absence of labile protons.

Pettersson (1975) obtained promising results with a ketocaine solution in patients undergoing skin grafting. These results stimulated us to study a new formulation combining ketocaine with isopropanol, glycerol and water called A 2337, and a clinical trial in 86 patients was reported by Pontén and Ohlsén in 1977. The analgesia produced by the topical application of A 2337 was very satisfactory for cutting split skin grafts and the simple technique seemed to be of great value. The present study of a larger number of patients was performed using the formulation called A 2358 containing ketocaine (base) 0.100 g ml^{-1}, isopropanol 0.450, glycerol 0.120, water 0.250 and acetic acid 0.001 g ml^{-1}. This is the same composition as A 2337 with the small amount of acetic acid added

---

LENNART OHLSÉN, M.D., Department of Plastic Surgery; SÖREN ENGLESSON, M.D., Department of Anaesthesiology; University Hospital, S-750 14 Uppsala, Sweden.

0007-0912/80/040413-05 $01.00

© Macmillan Journals Ltd 1980

as an antioxidant. The proportions are such as to yield a saturated solution of ketocaine. All the solvent ingredients are necessary for efficacy as a surface anaesthetic, the relative proportions giving the best result of an interaction between the base and the solvent whereby the diffusion rate of the compound increases.

METHODS

A 2358 (Ane-Pad) has been tested on 173 patients, 115 men and 58 women. Their ages ranged from 14 to 86 yr (average 50.4 yr). Patients known to be pregnant were excluded.

The patients were classified with respect to the anaesthetic risk using the A.S.A. classification of physical status. Thirty-two patients (18.5%) were in group I and 79 (45.7%) in group II. Fifty-five (31.8%) were in group III and seven (4.0%) in group IV (fig. 2).

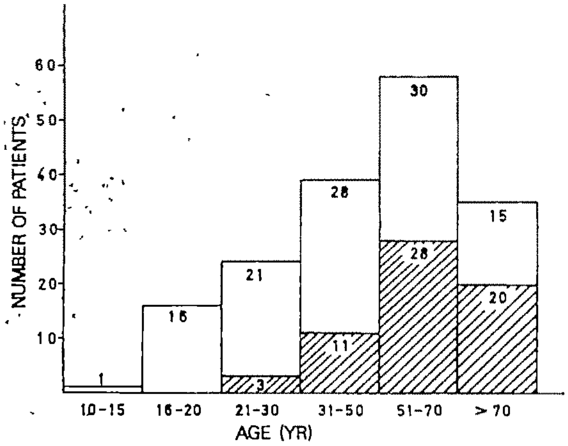


FIG. 2. Age and risk groups. In each age group, patients are divided into two subgroups: risk groups I–II (open) and risk groups III–IV (hatched).

Twenty-six patients had a history of allergic reactions, but not to local anaesthetic drugs. Premedication was used in 119 patients (68.8%); 111 received diazepam 5–10 mg orally and five were given diazepam with pentazocine. One patient received diazepam and pethidine. Another received promethazine and pethidine, and one was given morphine and hyoscine.

Ane-Pad consists of 90% cotton wool and 10% viscous cellulose compressed to a felt-like consistency. The pad measures 10.5 × 12 cm, contains 5.3 ml of the sterile anaesthetic solution and is enclosed in heat-sealed aluminium foil (fig. 3). At room temperature the pad can be stored in the unbroken foil for 2 years without losing its pharmacological properties. After removal from the foil the pad was used immediately to avoid drying.

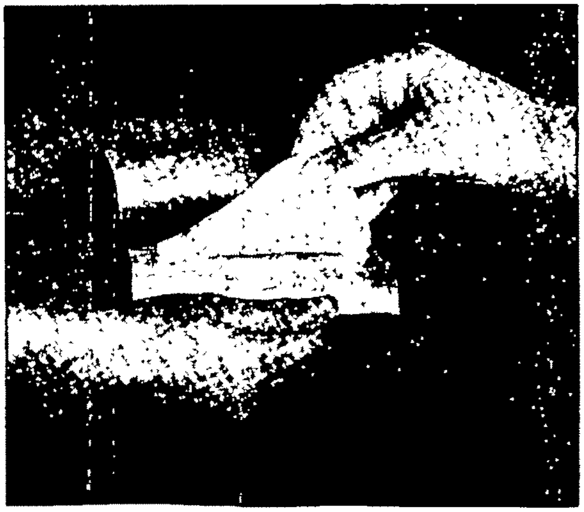


FIG. 3. The pad soaked in the anaesthetic compound is enclosed in foil.

The selected donor site was shaved and cleaned on the day before operation. Early in the morning the pad or pads were applied directly to the donor site. The pads were covered with an occlusive sheet taped to the skin and slight compression was obtained by an elastic bandage.

In 81 patients (46.8%) one pad was used, in 66 (38.2%) two pads; three to four pads in 21 patients (12.1%) and five to eight pads in five patients (2.9%).

The skin grafts were taken with a Brown electrodermatome or a knife and no technical problems were encountered. There was no obvious difference in bleeding or in the healing time of the donor site compared with skin grafts taken under general or local anaesthesia. The thickness of the grafts was preset on the dermatome to thinner than 0.43 mm (24 patients), 0.43–0.51 mm (139 patients) and 0.53–0.58 (five patients), while a hand-knife was used in five patients.

The area of the grafts varied. In 104 patients the area was less than 50 cm² but in the rest grafts up to and greater than 500 cm² were taken.

The most frequently used donor site was the thigh (131 patients). The leg was used in four patients, the hip in two, the upper arm in 26 and the forearm in 11 patients.

Since the pads were not removed until the patient was prepared for surgery the duration of the application varied considerably, ranging from less than 1 h to 10 h. The mean duration was 3 h 5 min.

Arterial pressure and heart rate were measured before the pad was applied and when the pad was removed for operation. In the five patients to whom a large number of pads were applied, the e.c.g. was examined hourly after the application until 3 h after the operation.

In 101 patients, venous blood samples were taken immediately after removal of the pads and 3 h later. The concentration of ketocaine was determined by means of gas chromatography and mass fragmentography (Berlin-Wahlén et al., 1977) at the Department of Analytical Chemistry, Astra Läkemedel AB, Södertälje, Sweden.

RESULTS

The pads rarely caused irritation. Only 18 patients (11.4%) stated that the pads caused a slight, transient, local irritation or a burning pain immediately after application. In a few cases this pain was quite intense but was always of short duration—sometimes only a few seconds and never more than a minute. This seemed to occur when the skin was not completely intact, in the presence of a small wound after shaving. This minor discomfort, however, was never a problem and no patient requested the removal of the bandage.

When the bandage was removed erythema or oedema, or both, was often visible in the application area. In 39 patients (22.5%) erythema was moderate to pronounced (table I) and in eight patients (4.7%) there was moderate to pronounced oedema. Using the χ^2 test there was a significant association ($P < 0.001$) between the degree of erythema and the duration of application. Oedema, however, was not related to the application time. There appeared to be a relationship between the degree of erythema and the anaesthetic effect, although this could not be verified statistically.

TABLE I. *Appearance of oedema or erythema in the application area. The figures refer to the number of patients* (%)

	None	Slight	Moderate	Pronounced
Oedema	94 (54.3)	71 (41.0)	7 (4.1)	1 (0.6)
Erythema	42 (24.3)	92 (53.2)	34 (19.6)	5 (2.9)

When the skin graft was cut, 114 patients (65.9%) experienced no pain and only felt the pressure of the dermatome. Forty-three patients (24.9%) experienced some pain, but they did not object when the skin graft was cut, only mentioning the slight discomfort afterwards. In 13 patients (7.5%) the pain was described as moderate, but the operation could be completed without any further local or general anaesthesia. One patient (0.6%) described the pain as severe, but allowed the skin graft to be cut without additional anaesthesia. In two patients (1.1%) anaesthesia was supplemented by a local anaesthetic drug. In one of these two patients the pad had been applied for only 35 min—insufficient to produce adequate anaesthesia. Thus it was possible to perform the planned operation in 98.9% of patients and in 90.8% the applied ketocaine formulation provided completely satisfactory surface anaesthesia. The local anaesthetic effect could be related to neither duration nor premedication.

The blood concentration of ketocaine (table II) increased with the number of pads applied and also with the duration of application. This increase was observed for 5 h and then a decrease occurred even in the presence of the pads, probably because of metabolism or alteration of the anaesthetic formulation. Three hours after removal of the pads the blood concentration of ketocaine had decreased.

None of the 173 patients found Ane-Pad disagreeable and no allergic reactions were noticed. No patient reported anything which could be interpreted as a toxic effect. No clinically significant change in arterial pressure or heart rate was detected. The

TABLE II. *The blood concentration of ketocaine (ng ml^{-1}) determined by mass fragmentography in the blood of 84 patients, immediately after removal of the pads, and then 3 h later* (*values in parentheses*)

	Duration of application (h)						
Pad	1–2 ($n = 9$)	2–3 ($n = 39$)	3–4 ($n = 17$)	4–5 ($n = 8$)	5–6 ($n = 9$)	6–7 ($n = 1$)	9–10 ($n = 1$)
8 ($n = 1$)			416 (138)				
6 ($n = 1$)		506 (844)					
4 ($n = 3$)		106.0 (136.5)	539 (331)				
3 ($n = 8$)	119 (23)	232.5 (93.0)	250.0 (106.5)		207.0 (161.7)		
2 ($n = 34$)	111.7 (38.0)	92.5 (63.0)	108.4 (85.5)	239.2 (111.2)	329.3 (151.7)		
1 ($n = 37$)	55.4 (30.0)	70.6 (40.4)	73.5 (72.0)	195.5 (79.0)	44.0 (40.0)	147 (139)	91 (7)

serial e.c.g. recorded in five patients did not show any adverse changes.

DISCUSSION

The results of the present study indicate that after cutaneous application of Ane-Pad the nerve endings are sufficiently blocked to permit the removal of split skin grafts. The average thickness of a split skin graft includes at least 50–75% of the thickness of the skin. In animal experiments (Åkerman, 1978) the distribution of ^{3}H-labelled ketocaine in the skin was studied after application of A 2358. Radioactivity was detected at all levels of the skin with large concentrations in the stratum corneum and rapidly decreasing activity in the deeper underlying tissue.

It should be pointed out that Ane-Pad causes analgesia rather than the elimination of all sensory modalities. The epicutaneous application of the ketocaine formulation gives rise to a loss of, or a decrease in, the perception of normally painful stimuli and a suppressed excitability of cutaneous C receptors (L. Juhlin, personal communication; Hallin, 1974). We have observed that the pressure of the dermatome was always felt, but that sensitivity to touch was distinctly reduced. However, touching and moving a hair in the area treated with Ane-Pad was felt very distinctly, presumably because the hair follicles penetrate to a dermal depth not reached by the anaesthetic. When testing for analgesia by pinprick, the pressure of the pin could be appreciated, but not pain. Sensitivity to cold was either unchanged or reduced, but sensitivity to warmth was increased. A luke-warm water wash of the test area was described as a very unpleasant experience.

The duration of application is of importance, at least 1 h being necessary to obtain adequate analgesia. The duration of analgesia was several hours and our patients complained much less of pain from the donor site immediately after operation and requested less analgesic than patients who had received general anaesthesia. We have noticed that occasionally the effect can last for 24 h or even more. After the application of A 2358 containing ^{3}H-labelled ketocaine to animals (Åkerman, 1978), the half-life of the radioactivity in the skin was found to be 5–5.5 h while 10–15% of the activity remained in the tissue after 1 day.

The maximum blood concentration of ketocaine was 844 ng ml^{-1} after the application of six pads. This should be compared with the blood concentrations of 1.01–2.59 μg ml^{-1} noted 0.5 h after brachial plexus block with ketocaine hydrochloride 300 mg in 10 patients (Berlin-Wahlén et al., 1977). As absorption is small after epicutaneous application, this technique appears to be free from toxicological effects. Our patients suffered no systemic side-effects after application of Ane-Pad.

In most patients there was some local erythema and slight oedema in about 50%. The degree of erythema increased with the duration of application and reached a maximum after 3 h. The erythema or oedema were, however, an advantage to the surgeon as they depicted the anaesthetic area. Both erythema and oedema disappeared more rapidly than the anaesthetic effect.

Usually, the skin on a donor site recovers very slowly. Full stability and thickness is not achieved for several months. We have observed that if Ane-Pad is applied during this time it will cause local irritation and even blister formation.

In a previous clinical study in our hospital (Pontén and Ohlsén, 1977) A 2337 was studied in 86 similar patients. The addition of acetic acid as antioxidant did not adversely influence the efficacy of Ane-Pad. Therefore, we have now studied a total of 259 patients. This new technique is a simple, time-saving and effective form of anaesthesia. The absence of systemic side-effects is of special advantage in old or seriously ill patients.

REFERENCES

Adriani, J., and Dalili, H. (1971). Penetration of local anesthetics through epithelial barriers. *Anesth. Analg., (Cleve.)*, **50**, 834.

Åkerman, B. (1978). Percutaneous local anaesthesia. Problems—solutions. *Acta Anaesthesiol. Scand.*, Suppl. 70, 90.

Appiani, L., and Laveneziana, D. (1966). Il blocko peridurale con chetocaina (Rec. 7–0518). *Anest. Rianim.*, **3**, 441.

Berlin-Wahlén, A., Hogberg, L., Lindgren, J. E., and Vecchietti, M. (1977). Determination of ketocaine blood concentrations following brachial plexus block and epicutaneous administration. *Acta Pharmacol. Suec.*, **14**, 425.

Brechner, V. L., Cohen, D. D., and Pretsky, I. (1967). Dermal anesthesia by the topical application of tetracaine base dissolved in dimethyl sulfoxide. *Ann. N.Y. Acad. Sci.*, **141**, 524.

Dalili, H., and Adriani, J. (1971). The efficacy of local anaesthetics in blocking the sensations of itch, burning, and pain in normal and "sunburned" skin. *Clin. Pharmacol. Ther.*, **12**, 913.

Hallin, R. G. (1974). Blocking effects of a topical anaesthetic composition containing ketocaine as cutaneous C receptor responses in alert man. *Acta Anaesthesiol. Scand.*, **18**, 306.

Kligman, A. M. (1965). Topical pharmacology and toxicology of dimethyl sulfoxide. *J.A.M.A.*, **193**, 140.

Monash, S. (1957). Topical anaesthesia of the unbroken skin. *A.M.A. Arch. Dermatol.*, **76**, 752.

Pettersson, L. O. (1975). Perkutan anestesi vid tagning av delhudstransplantat. *Läkartidningen*, **27**, 2822.

Piccolo, A. (1964). Sull'uso in Chirurgia di un nuovo anestetico locale: il Rec 7/0518. *Recept. Med.*, **3**, 61.

Pontén, B., and Ohlsén, L. (1977). Skin surface application of ketocaine to provide local anaesthesia for cutting split skin grafts. *Br. J. Plast. Surg.*, **30**, 251.

Rubin, L. F. (1975). Toxicity of dimethyl sulfoxide, alone and in combination. *Ann. N.Y. Acad. Sci.*, **243**, 98.

Setnikar, I. (1966). Ortho-substituted β-phenoxyethylamino derivatives. *Arzneim. Forsch.*, **16**, 1025.

NOUVELLE FORMULATION D'ANESTHESIQUE POUR APPLICATION EPICUTANEE ESSAYEE POUR LA COUPE DE GREFFES EPIDERMIQUES

RESUME

Une nouvelle formulation d'agent d'anesthésie locale: Ane-Pad (A 2358, Astra Läkemedel AB) pour application sur la peau a été essayée lors du prélèvement de greffes épidermiques. Ane-Pad est un mince tampon de coton, contenant une solution de kétocaïne à 10% dans un mélange solvant d'isopropanol, de glycérol et d'eau. Le tampon a été utilisé sur le lieu du prélèvement de 173 patients, avec un temps d'application minimum d'une heure avant l'intervention. Dix-huit patients se sont plaints d'une irritation légère et transitoire immédiatement après l'application. Après retrait du tampon, on a constaté de l'érythème sur 39 patients et un oedème sur huit autres. Sur 157 patients (90,8%), l'analgésie a été adéquate. Deux patients (1,1%) ont dû recevoir un complément d'anesthésie. La concentration de kétocaïne dans le sang a été mesurée sur 101 personnes et elle n'a pas dépassé 850 ng ml^{-1}. Il n'y a eu aucun effet secondaire systémique.

NEUES ANÄSTHESIEMITTEL ZUR AUFTRAGUNG AUF DIE HAUT WURDE ANLÄSSLICH DER ENTFERNUNG GESPATENER HAUTVERPFLANZUNGEN GETESTET

ZUSAMMENFASSUNG

Ane-Pad (A 2358, Astra Läkemedel AB), eine neue Lokalanasthesieformel zur Auftragung auf die Haut wurde bei der Entfernung von gespaltenen Hautverpflanzungen getestet. Ane-Pad ist ein dunner Wattebausch mit einer Lösung aus 10%igem Ketocain in einer Mischung aus Isopropanol, Glyzerol und Wasser. Solche Wattebausche wurden auf die Hautspendestellen von 173 Patienten gelegt, und zwar wenigstens 1 Stunde lang vor der Operation. Achtzehn Patienten empfanden unmittelbar nach der Auftragung des Wattebausches eine leichte, vorübergehende Hautirritation. Nach Entfernung des Bausches zeigte sich Hautrötung bei 39 Patienten, und Ödembildung bei 8 Patienten. Bei 157 Patienten (90,8%) erwies sich die Schmerzlinderung als ausreichend. Zwei Patienten (1.1%) benötigten zusatzliche Anesthesie. Die Ketocain-Konzentration im Blut wurde bei 101 Patienten gemessen und überschritt nicht 0,850 ng ml^{-1}. Es gab keine systemischen Nebenerscheinungen.

FORMULACION ANESTETICA NUEVA PARA APLICACION EPICUTANEA COMPROBADA PARA EL CORTE DE INJERTOS PARTIDOS DE PIEL

SUMARIO

Se hicieron ensayos con Ane-Pad (A 2358, Astra Läkemedel AB), una nueva fórmula de anestesia local para su aplicación en la piel respecto de la remoción de injertos partidos de piel. Ane-Pad consiste en un tampón de algodón delgado que contiene una solución de quetocaina base al 10% en una mezcla solvente de isopropanol, de glicerol y de agua. Se usó este tampón en los lugares de los donantes en 173 pacientes con un tiempo mínimo de aplicación de 1 h antes de la operación. Diez y ocho pacientes se quejaron de una irritación ligera y pasagera imediatamente después de la aplicación. Se comprobó, después de la remoción del tampón, que 39 pacientes tenían eritema y ocho edema. En 157 pacientes (90,8%), la analgesia era adecuada. Dos pacientes (1,1%) necesitaron una anestesia adicional. Se midió la concentración de quetocaina en la sangre de 101 pacientes y ésta no excedía de 850 ng ml^{-1}. No hubo efectos colaterales sistémicos.

Br. J. Anaesth. (1980), **52**, 419

COMPARISON OF CARBONATED BUPIVACAINE AND BUPIVACAINE HYDROCHLORIDE FOR EXTRADURAL ANAESTHESIA

D. T. Brown, D. H. Morison, B. G. Covino and D. B. Scott

SUMMARY

A double-blind comparison of carbonated bupivacaine and bupivacaine hydrochloride in extradural anaesthesia was performed in 40 patients. No significant differences in the onset times, sensory blockade, motor blockade and duration of anaesthesia were demonstrated. Carbonated bupivacaine does not appear to offer any advantage over the hydrochloride salt for extradural anaesthesia.

Carbonated local anaesthetic agents may have advantages over the hydrochloride salts because of their shorter latency and improved sensory and motor blockade. Bromage and colleagues (1967) reported a more rapid onset of anaesthesia and more profound sensory and motor blockade following the extradural administration of lignocaine CO_2 and prilocaine CO_2. Moreover, in brachial plexus block Bromage and Gertel (1970) observed a marked decrease in the onset time of anaesthesia from a mean value of 14 min with lignocaine HCl to 8 min with lignocaine CO_2.

Bupivacaine is a long-acting agent which usually demonstrates a slow onset of action and minimal motor blockade. For example, Bromage and Gertel (1970) reported an average onset time of 23 min for bupivacaine compared with 14 min for lignocaine following brachial plexus blockade with these agents. Carbonation of bupivacaine has been attempted as a means of reducing the latency and Eckstein and co-workers (1978) observed a more rapid onset of extradural anaesthesia with bupivacaine CO_2. Unfortunately, these workers did not study the hydrochloride and carbonated salts of bupivacaine under controlled conditions. The present double-blind study compared the anaesthetic properties of bupivacaine HCl and CO_2 in extradural blockade.

PATIENTS AND METHODS

Forty non-pregnant and otherwise healthy women undergoing abdominal gynaecological surgery were studied. All were premedicated with diamorphine 5 mg and atropine 0.6 mg i.m. approximately 45 min before anaesthesia. In each patient the extradural space was identified at L2–3 using a loss of resistance technique and a catheter inserted and positioned with the 9-cm mark at the skin surface. All the catheters were inserted by the same anaesthetist. Before the local anaesthetic was injected the patients were turned supine and horizontal. The patients were divided randomly into two groups, similar in age, height and weight (table I). One group received 0.5% bupivacaine HCl 20 ml and the second group received 0.44% bupivacaine CO_2 20 ml. These solutions contain equal amounts of bupivacaine base.

TABLE I. *Mean age, height and weight, with SEM, of patients receiving either carbonated bupivacaine or bupivacaine hydrochloride. Differences between groups not significant* ($P > 0.05$)

	Bupivacaine CO_2	Bupivacaine HCl
Age (yr)	41.4	42.8
	1.5	2.4
Height (cm)	161.5	161.6
	1.4	1.8
Weight (kg)	67.0	59.4
	3.5	2.0

The onset and spread of the sensory block and the degree of motor block were assessed every 2 min for 30 min after the injection of bupivacaine but before the start of surgery. The arterial pressure and heart rate were measured at 5-min intervals. All the assessments in all the patients were made by the same observer who was unaware which drug had been given.

The dermatome level of sensory block was tested by pin-prick. Analgesia was defined as the loss of

---

D. T. Brown, F.F.A.R.C.S.; D. B. Scott, M.D., F.R.C.P.E., F.F.A.R.C.S.; Department of Anaesthesia, The Royal Infirmary, Edinburgh EH3 9YW. D. H. Morison, M.B., CH.B., F.R.C.P.(C), Department of Anaesthesia, McMaster University, Hamilton, Ontario, Canada. B. G. Covino, M.D., Department of Anesthesia, University of Massachusetts, Medical Center, Worcester 01605, Ma., U.S.A.

0007-0912/80/040419-04 $01.00

© Macmillan Journals Ltd 1980

sensation of sharpness and anaesthesia as the loss of sensation of touch. The upper extent of the block was noted, but the lower level was not determined.

Motor block was scored on a scale of 0–3. A score of 0 was awarded when there was no motor block, 1 when there was objective evidence of muscle weakness in the legs, 2 when the patient could not raise her heels from the table and 3 when she could not bend her knees to 90°. Thirty minutes after the injection of bupivacaine the patient was anaesthetized with thiopentone and the surgical procedure commenced. During the operation light general anaesthesia was maintained with nitrous oxide in oxygen. Halothane was added to the inspired gas if required. At the completion of surgery, the patient recovered consciousness rapidly and the sensory and motor blocks were assessed at intervals. "Two-segment regression" could not be measured because several of the blocks had regressed more than two segments by the end of surgery, so four-segment regression times and the time until sensory blockade was not detectable in the thoracic dermatomes were calculated. The patient's ability to elevate her heels from the bed was taken as the end-point of motor blockade. The statistical significance of differences between the data from the two groups of patients was determined using Student's *t* test.

RESULTS

The mean onset times for sensory and motor blockade are shown in table II. The time to the initial onset of detectable sensory loss was 6.7 min for bupivacaine CO_2 compared with 7.2 min for bupivacaine HCl. The time until maximum spread of analgesia (loss of sharpness to pin-prick) was 19.4 min for bupivacaine CO_2 compared with 20.6 min for bupivacaine HCl. Similarly, the time for maximum spread of anaesthesia (loss of touch sensation) was 22.2 min for bupivacaine CO_2 and 22.7 min for bupivacaine HCl. The mean onset time for a motor block score of 1 (first sign of weakness) was 8.4 min for bupivacaine CO_2 compared with 8.5 min for bupivacaine HCl. A motor block of 2 (unable to raise heels) was reached in 14.7 min using bupivacaine CO_2 and in 16.4 min with bupivacaine HCl. Motor block of 3 (unable to bend knees) was reached in 20.7 min with bupivacaine CO_2 and in 22.6 min using bupivacaine HCl. The mean onset times for bupivacaine CO_2 were all shorter than the equivalent times for bupivacaine HCl, but the differences were not statistically significant.

TABLE II. *Mean onset time (min) of sensory and motor blocks. Differences between groups not significant* ($P > 0.05$)

	Analgesia		Anaesthesia	Motor score		
	Initial onset	Max. spread	Max. spread	1	2	3
Bupivacaine CO_2	6.7	19.4	22.2	8.4	14.7	20.7
SEM	0.6	1.3	1.2	0.7	1.1	2.1
n	20	20	19	20	18	11
Bupivacaine HCl	7.2	20.6	22.7	8.5	16.4	22.6
SEM	0.6	1.5	1.3	0.6	1.3	1.5
n	20	20	19	20	16	11

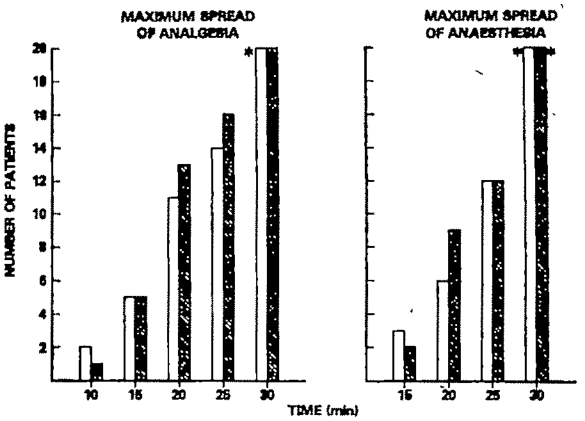


FIG. 1. Time taken to maximum spread of extradural analgesia (loss of sensation to pin-prick) and anaesthesia (loss of touch sensation) in 20 patients receiving bupivacaine HCl (clear columns) and 20 patients receiving bupivacaine CO_2 (cross-hatched columns). * Three patients in each graph may not have reached maximum spread by 30 min.

Figure 1 compares the onset of maximum analgesia and anaesthesia. The pattern of onset is similar for both drugs. The asterisks indicate that three patients in each group did not reach maximum spread within 30 min because the dermatome level changed between 28 and 30 min. The onset pattern of the motor blocks was similar for the two groups. All the patients reached a motor score 1, 18 of the bupivacaine CO_2 and 16 of the bupivacaine HCl reached a score of 2, and only 11 of each group reached a score of 3.

The time required for the blocks to reach specified dermatome levels showed no advantage with either solution. Bupivacaine 20 ml of either type could only be relied on to produce adequate analgesia for lower abdominal operations and at least 20 min was required for the onset of the block.

The duration of the blocks is shown in table III. There was no significant difference between the groups, the average duration of thoracic analgesia being more than 5 h and of motor block more than 4 h.

TABLE III. *Duration (min) of analgesia and motor block. Differences between groups not significant* ($P > 0.05$)

	Analgesia		Motor
	Four-segment regression	Regression to lumbar dermatomes	Regression to 1
Bupivacaine CO_2	225.7	330.1	247.7
SEM	18.5	17.6	16.9
n	20	20	20
Bupivacaine HCl	221.8	332.8	254.2
SEM	14.1	14.7	21.2
n	20	20	20

The changes in arterial pressure and heart rate in each group were similar. In both groups the systolic arterial pressure decreased by between 10 and 20 mm Hg within 10 min compared with the pressures before anaesthesia. The CO_2 group had a slightly greater decrease in systolic pressure and at 5 min there was a significant difference. Diastolic pressure showed a maximum decrease of just over 10 mm Hg and there was no significant difference between the groups. The mean heart rates showed only small changes in either group.

DISCUSSION

The study showed that carbonated bupivacaine had a slightly more rapid onset of action than bupivacaine hydrochloride but did not produce better sensory or motor blockade.

The combination of carbon dioxide with local anaesthetics may potentiate their action by a direct depressant effect of carbon dioxide on the axon, or by increasing the concentration of local anaesthetic inside the nerve trunk and by converting local anaesthetic to the active cation at the site of action inside the nerve (Catchlove, 1972). Carbonation may increase blood flow at the site of injection and so increase the removal of anaesthetic from the nerves.

The onset times of extradural anaesthesia with carbonated salts of lignocaine and prilocaine have been shown to be 30% shorter than with the hydrochloride salts (Bromage et al., 1967) and improved sensory and motor blockade were reported also.

Bupivacaine, with its relatively slow onset, would seem to be a suitable agent for carbonation. However, in this double-blind study the differences between the carbonated and hydrochloride solutions were neither clinically nor statistically significant. Reports by Bromage (1978) and Eckstein and co-workers (1978) have shown that the onset time with bupivacaine CO_2 is only very slightly less than with bupivacaine HCl. In addition, these studies demonstrated a shorter duration of effect of bupivacaine CO_2, but this was not confirmed by our investigation.

Nevertheless, an enhanced rate of block can be demonstrated *in vitro* in an isolated nerve with bupivacaine CO_2 (Catchlove, 1973). The failure to demonstrate a significant difference between bupivacaine CO_2 and bupivacaine HCl in the present study may indicate that the CO_2 is buffered before it can exert a significant effect on an agent which has an intrinsically slow onset time. In addition, the absorption of bupivacaine may be increased by CO_2, which would decrease the amount of drug available at the site of action. Appleyard and colleagues (1974) demonstrated that extradural blockade with bupivacaine CO_2 produced greater plasma concentrations of bupivacaine than bupivacaine HCl, although they did not compare the clinical effects of the nerve block.

It must be emphasized that the present study was concerned with extradural block only and different results might be obtained at other sites of injection. It may be the complicated mechanism involved in producing an extradural block (Bromage, 1978) that nullifies the enhancing effects of carbonation.

Of some clinical interest was the generally disappointing performance of 0.5% bupivacaine in extradural block for surgical procedures. Its relative sparing of motor function, so useful in providing continuous analgesia in labour, is a disadvantage in surgery and its very long latency (in six of 40 patients maximal spread still had not occurred after 30 min) is a particular handicap.

REFERENCES

Appleyard, T. N., Witt, A., Atkinson, R. E., and Nicholas, A. D. G. (1974). Bupivacaine carbonate and bupivacaine hydrochloride: a comparison of blood concentrations during epidural blockade for vaginal surgery. *Br. J. Anaesth.*, **46**, 530.

Bromage, P. R. (1978). *Epidural Analgesia*, 1st edn, pp. 319, 119. Philadelphia, London, Toronto: W. B. Saunders Company.

—— Burfoot, M. F., Crowell, D. E., and Truant, A. P. (1967). Quality of epidural blockade. III: Carbonated local anaesthetic solutions. *Br. J. Anaesth.*, **39**, 197.

Bromage, P. R., and Gertel, M. (1970). An evaluation of two new local anaesthetics for major conduction blockade. *Can. Anaesth. Soc. J.*, **17**, 557.

Catchlove, R. F. H. (1972). The influence of CO_2 and pH on local anaesthetic action. *J. Pharmacol. Exp. Ther.*, **181**, 298.

—— (1973). Potentiation of two different local anaesthetics by carbon dioxide. *Br. J. Anaesth.*, **45**, 471.

Eckstein, K. L., Vicente-Eckstein, A., Steiner, R., and Missler, U. (1978). Klinische Erprobung von Bupivacaine-CO_2. *Anaesthesist*, **27**, 1.

COMPARAISON ENTRE LA BUPIVACAINE CARBONATEE ET LE CHLORHYDRATE DE BUPIVACAINE POUR L'ANESTHESIE EXTRADURALE

RESUME

On a fait sur 40 malades une comparaison à double inconnue entre la bupivacaïne carbonatée et le chlorhydrate de bupivacaïne utilisés pour l'anesthésie extradurale. On n'a constaté aucune différence importante dans les temps de l'induction, du blocage sensitif, du blocage moteur ou la durée de l'anesthésie. La bupivacaïne carbonatée ne semble pas présenter d'avantage par rapport au sel de chlorhydrate lors d'une anesthésie extradurale.

VERGLEICH ZWISCHEN KARBONISIERTEM BUPIVACAIN UND BUPIVACAIN-HYDROCHLORID FÜR EINE EXTRADURALE ANÄSTHESIE

ZUSAMMENFASSUNG

Ein Doppelblindvergleich zwischen karbonisiertem Bupivacain und Bupivacain-Hydrochlorid bei extraduraler Anästhesie wurde bei 40 Patienten vorgenommen. Wesentliche Unterschiede im Wirkungsbeginn, sensorischer Blockierung, motorischer Blockierung und Narkosedauer wurden nicht beobachtet. Karbonisiertes Bupivacain scheint keine Vorteile bei extraduraler Anästhesie gegenüber dem Hydrochlorsalz zu besitzen.

COMPARACION DE LA BUPIVACAINA CARBONADA Y DEL HIDROCLORURO DE BUPIVACAINA PARA LA ANESTESIA EXTRADURAL

SUMARIO

Se procedió a una comparación doble-ciega de la bupivacaina carbonada y el hidrocloruro de bupivacaina en 40 pacientes sometidos a una anestesia extradural. No se registraron diferencias algunas en el momento de efectividad de la anestesia, en el bloqueo sensorial, en el bloqueo motor y en la duración de la anestesia. La bupivacaina carbonada no parece ofrecer ventaja alguna sobre la sal de hidrocloruro en lo que se refiere a la anestesia extradural.

Br. J. Anaesth. (1980), 52, 423

PLACENTAL TRANSFER AND NEONATAL EFFECTS OF DIAZEPAM WHEN ADMINISTERED TO WOMEN JUST BEFORE DELIVERY

C. B. McAllister

SUMMARY

Diazepam 10 mg i.v. was administered to 23 patients (test group) just before delivery. The umbilical cord blood was analysed for diazepam and the well-being of neonates in the test group and in a suitable control group ($n = 32$) was compared using analysis of covariance. Diazepam was detected in neonatal blood about 0.5 min following its administration to mothers. No significant differences in neonatal well-being were detected between the two groups. However, a highly significant inverse relationship was found between the rectal temperature of the newborn and the concentration of diazepam in umbilical cord blood.

Diazepam is used to advantage in labour, producing relaxation of pelvic musculature and control of hyperventilation (Erkkola, Kanto and Sellman, 1974), relief of emotional distress (Bepko, Lowe and Waxman, 1965) and amnesia (Mundow and Long, 1974). Diazepam has been detected at birth in umbilical cord blood from 12 min to 7 h following the administration of 10 mg to the mother (Cavanagh and Condo, 1964; De Silva, D'Arconte and Kaplan, 1964; Bepko, Lowe and Waxman, 1965; Shannon et al., 1972; Mandelli et al., 1975; Gamble et al., 1977). Adverse effects on the newborn of the administration of diazepam in labour have been reported occasionally. Joyce and Kenyon (1972) associated neonatal hypothermia with the administration of large doses of diazepam for the control of pre-eclamptic toxaemia. McCarthy, O'Connell and Robinson (1973) found a relationship between the blood concentrations of diazepam in the newborn and serious neonatal distress. The administration of diazepam (mean dose 26 mg) during normal labour has been associated with poor muscle tone in the newborn (Flowers, Rudolph and Desmond, 1969). As a result the need for caution in the use of diazepam in labour has been stressed (Rowlatt, 1978; Woods and Malan, 1978).

It might be assumed that postponing the administration of diazepam until a few minutes before delivery would avoid the transfer of significant amounts of the drug to the fetus. As an accurate method for the determination of low concentrations of diazepam in biological media is available, the writer has determined if significant concentrations of the drug could be found in blood of the newborn and adverse neonatal effects (decrease in Apgar score, suppression of Moro reflex, difficulty in feeding and hypothermia) would occur when diazepam 10 mg was given i.v. less than 12 min before delivery.

PATIENTS AND METHODS

Sixty-five patients were studied. Fifty-five formed the first two groups; the sequence of patients was interrupted only to exclude those who had had an abnormal pregnancy. Twenty-three patients to whom diazepam 10 mg i.v. had been administered less than 12 min before delivery formed a test group; 32 patients to whom diazepam had not been administered formed the control group (table I). Pethidine and, in many instances, promethazine, promazine or levallorphan were administered during labour. The third group (table II), comprising 10 patients to whom diazepam 10 mg i.v. had been administered less than 12 min before delivery, was used to study the distribution of diazepam between fetal arterial and fetal venous blood ("distribution group").

Blood sampling

Blood samples were obtained from infants in the test and distribution groups only. Upon delivery the umbilical cord was clamped in two places and, in the case of infants in the test group, severed. A sample of mixed cord blood was obtained by draining the section between the clamps into a heparinized tube. Separate arterial and venous cord blood samples

---

C. B. McAllister, M.Sc., Department of Pharmacology, University College Cork, Ireland.

Present address: Department of Clinical Pharmacology, Medical School, Vanderbilt, University, Nashville 37232, U.S.A.

0007-0912/80/040423-05 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Data for a group of 23 patients to each of whom diazepam 10 mg i.v. had been administered towards the end of labour (the test group) and for a group of 32 patients to whom it had not (the control group). (A–D) = administration to delivery interval; * Moro reflex: absent = 0, feeble = 1, good = 2*

No. of variable		Test group		Control group	
		Mean	SD	Mean	SD
1	Age (yr)	29.6	4.8	27.9	6.6
2	Height (m)	1.63	0.04	1.60	0.06
3	Weight (kg)	67.2	7.2	64.2	9.0
4	Parity	1.4	1.4	2.2	2.5
5	Duration of labour (h)	4.30	1.75	6.18	3.91
6	Gestational age (week)	40.2	0.82	40.2	1.31
7	Birth weight (kg)	3.53	0.33	3.46	0.47
8	Pethidine (total amount) (mg)	82.6	49.1	75.0	31.1
9	Pethidine (total dose) (mg kg^{-1})	1.24	0.76	1.19	0.52
10	Promethazine (total amount) (mg)	50.0	30.2	39.2	30.5
11	Promazine (total amount) (mg)	15.2	23.5	7.8	18.5
12	Levallorphan (total amount) (mg)	0.05	0.26	0.18	0.29
13	Tobacco smoker (%)	17.0	39.0	47.0	51.0
14	Dose of diazepam (mg kg^{-1})	0.15	0.01	—	—
15	(A–D) of diazepam (min)	1.97	2.91	—	—
16	Cord concn of diazepam (ng ml^{-1})	248	327	—	—
17	Apgar score at 1 min	9.7	0.8	9.8	0.6
18	Apgar score at 5 min	9.9	0.5	10.0	0.2
19	Moro reflex*	1.9	0.3	1.9	0.3
20	Rectal temperature at 30 min (°F)	98.65	0.56	98.73	0.49

TABLE II. *Concentrations of diazepam in fetal arterial and venous blood at delivery following administration of 10 mg i.v. to the mother*

Patient no.	Dose of diazepam (mg kg^{-1})	(A–D) (min)	Arterial concn (ng ml^{-1})	Venous concn (ng ml^{-1})	Ratio venous/art. concn
1	0.14	3.0	3.7	6.7	1.80
2	0.15	4.0	144.3	295.1	2.04
3	0.13	5.0	118.6	426.9	3.60
4	0.14	0.2	507.3	742.4	1.46
5	0.14	10.0	336.5	610.4	1.81
6	0.13	5.0	237.1	669.5	2.82
7	0.15	3.0	31.5	276.0	8.76
8	0.15	7.0	552.2	1254.8	2.27
9	0.16	7.0	261.1	1230.3	4.72
10	0.14	1.6	235.4	1095.1	4.65
Mean	0.14	4.6	242.8	660.7	3.39

(obtained by syringe from vessels in the clamped section) were taken from patients in the distribution group. The blood was centrifuged and the plasma stored at 4 °C and analysed within 2 days. Under these conditions the plasma concentration of diazepam does not change (Gamble et al., 1975).

Chemical analysis

The method used for the extraction of diazepam from plasma was a modification of that used by Zingales (1973). On the basis of previous reports, it was not expected that the metabolite of diazepam, N-desmethyl diazepam, would be present in the blood samples (Idanpaan-Heikkila et al., 1971). This compound would have interfered with the gas–liquid chromatographic (g.l.c.) analysis of diazepam. Prazepam (7-chloro-1-cyclopropylmethyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one) was used as internal standard for extraction and g.l.c.

A suitable amount of prazepam was dissolved in 1 ml of plasma from cord blood and toluene : isoamyl alcohol (96 : 4) was used as extracting solvent. A back-extraction into HCl 6 mol litre^{-1} was then carried out. Following concentration of the final phase, the residue was collected (McAllister, 1977) and dissolved by vortex mixing in 100 μlitre of the extracting solvent. Injections of this solution (2 μlitre) were used in the g.l.c. analysis (McAllister, 1978).

Neonatal assessment

The 1- and 5-min Apgar scores and the rectal temperature at 30 min of the newborn were recorded in test and control groups. The head-drop Moro reflex was assessed on the following scale: absent (0), feeble (1), good (2). The occurrence of hyperbilirubinaemia and feeding difficulties in the first 24 h were noted.

Statistical methods

In order to ascertain whether the variables numbered 1–13 in table I and, in the case of the test group, the cord blood concentration of diazepam were related to the rectal temperature of the newborn in either the test or control groups, multiple regression analyses were carried out. The possible influences of the administration to delivery interval (A–D) of diazepam, the dose of diazepam per kg and the variables 1–13 on the cord blood concentration of diazepam were assessed likewise. Finally, the relationship between the administration of diazepam and rectal temperature was examined by covariance analysis of the test and control groups.

RESULTS

Placental transfer

Diazepam was detected in the cord blood of 20 neonates in the test group; this figure includes eight of 10 patients for whom (A–D) of diazepam was about 0.5 min.

The only variable which was found to have been related to the mixed cord blood concentration of diazepam was (A–D)—the longer the interval the greater the concentration ($P < 0.001$; fig. 1).

Data from the distribution group revealed that the venous and arterial concentrations of diazepam were correlated significantly ($P < 0.02$), the venous concentration being consistently greater than the corresponding arterial concentration. The mean venous/arterial ratio was 3.4. No relationship was found between this ratio and (A–D) of diazepam.

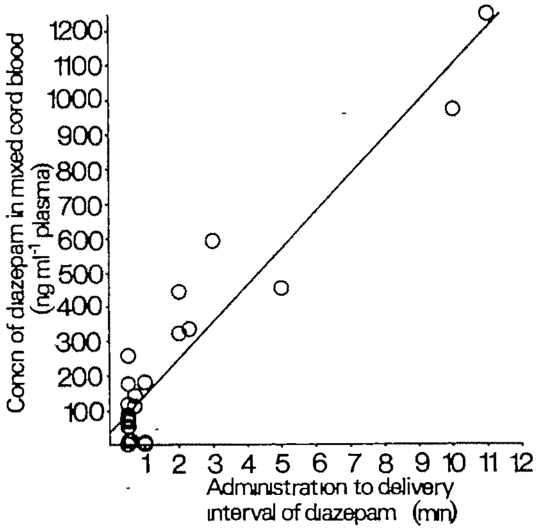


FIG. 1. The relationship between the maternal administration-to-delivery interval of diazepam and its concentration in the mixed umbilical cord blood of neonates.

Neonatal effects

With regard to Apgar scores and the frequency of feeble Moro reflex, feeding difficulties and hyperbilirubinaemia, there were no significant differences between the test and control groups. None of the variables 1–13 (table I) was related to the rectal temperature of the newborn and, while the mean rectal temperature in the test group was less than that in the control group, covariance analysis did not show this difference to be significant. However, regression analysis within the test group showed that the rectal temperature was related both to the mixed cord blood concentration of diazepam ($P < 0.01$; fig. 2) and to (A–D) of diazepam ($P < 0.05$).

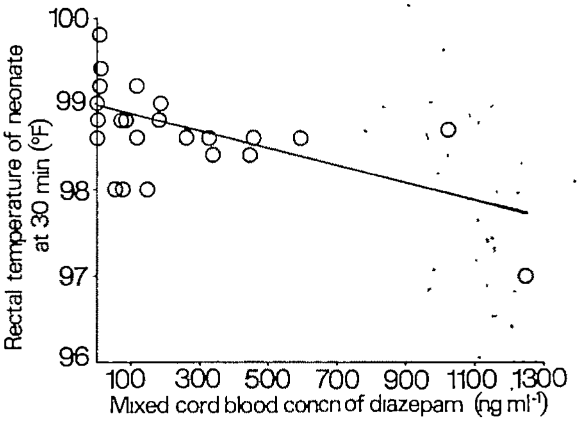


FIG. 2. The relationship between the concentration of diazepam in mixed umbilical cord blood and the 30-min rectal temperature of the newborn.

DISCUSSION

In the present study, diazepam was detected in the mixed cord blood of eight of 10 infants whose mothers had received this drug approximately 0.5 min before delivery. (There was one instance in which it was not detected when (A–D) was 1 min.) There are several reports of the detection of diazepam in cord blood within 1 h of its administration, as a single dose, to mothers. Erkkola, Kangas and Pekkarinen (1973) have reported its detection 5 min after the administration of 10 mg. Scher, Hailey and Beard (1972) have reported loss of beat-to-beat variation in fetal heart rate (a characteristic effect of diazepam) 1 min after the administration of 20 mg i.v. to mothers.

One minute would seem to be a reasonable estimate of the normal circulation time of blood (Bowman, Rand and West, 1968; Lippold and Winton, 1968). Towards the end of labour the cardiac output increases to about 9 litre min^{-1}. The time taken for blood to travel from a maternal vein to the placenta might, therefore, be estimated as less than 0.5 min. Thus, the present finding of diazepam in cord blood about 0.5 min after its i.v. administration to mothers is plausible and seems to be the earliest yet reported.

The mixed cord blood concentration of diazepam was found to have increased with (A–D) in the range 0.5–11 min. (A–D) is a major determinant of the area under the curve plotting the concentration in maternal plasma against time. As this area is an index of fetal exposure to the drug, the correlation between (A–D) of diazepam and its concentration in cord blood is to be expected. There is the probability that there was a net transfer of diazepam to the fetus for at least 11 min following its administration to the mother. Under similar circumstances, Mandelli and colleagues (1975) found approximately equal concentrations of diazepam in maternal and fetal blood at (A–D) 12 min. While Erkkola, Kangas and Pekkarinen (1973) measured diazepam concentrations in cord blood at (A–D) as little as 5 min, they did not report a significant trend in such concentrations. This probably resulted from the small number of patients with (A–D) less than 16 min in their study. Moore and McBride (1978) suggest that the fetus constitutes a slowly equilibrating tissue group in which diazepam does not reach equilibrium with the maternal systemic circulation for at least 5–10 h.

Concentrations of diazepam in the venous cord blood samples of the distribution group were consistently greater than the corresponding concentrations in arterial cord blood, reflecting the placental transfer of diazepam to the fetus. The mean ratio of these concentrations was 3.4 (mean (A–D) 4.6 min). A value for this ratio in the present range of (A–D) (0.5–11 min) does not seem to have been reported previously.

No significant differences were found between the test and control groups in terms of the measures of neonatal well-being which were used here. However, within the test group, the rectal temperature of the newborn was related inversely to the plasma concentration of diazepam in mixed cord blood, which in turn was related to (A–D). Cree, Meyer and Hailey (1973) found an impaired metabolic response to cold stress and an increased frequency of hypothermia in neonates of mothers who had received more than 30 mg of diazepam in the 15 h preceding delivery; the mean concentration of diazepam in cord plasma at delivery was 0.66 $\mu g\ ml^{-1}$. Owen, Irani and Blair (1972), who administered diazepam before or during labour, found a greater decrease in body temperature of neonates in their diazepam group in the first few hours after birth; the mean cord concentration of diazepam was 0.88 $\mu g\ g^{-1}$. However, Cree, Meyer and Hailey (1973) did not find any neonatal effect of diazepam in a group of patients for which the dose was or exceeded 30 mg in the 15 h preceding delivery, while the concentration of diazepam in cord plasma at delivery was 0.24 $\mu g\ ml^{-1}$. In the above studies diazepam had been administered some hours before delivery and the fetal exposure to the drug was greater than in the present study (10 mg of diazepam was administered on average 2 min before delivery).

The results of the present study suggest that, in a similar study conducted on a larger scale, the administration of diazepam would be found to be associated with decreases in neonatal temperature. The inverse relationship between the concentration of diazepam in the umbilical cord blood and rectal temperature of the newborn was found at concentrations of diazepam which, on the basis of previous reports, might be considered to be without effect.

ACKNOWLEDGEMENTS

The author wishes to thank Professor Kearney, Sr O'Brien and staff of the Erinville Hospital, Cork, and Dr L. S. Mundow for provision of blood samples and data, Professor M. A. Moran and Mr Michael Crowley, Statistics Department, University College Cork, for advice and aid in the computation of statistics, Roche Products Ltd, Welwyn Garden City, for a sample of pure diazepam and Warner-Lambert Ltd, Blackrock, Co. Dublin, for a sample of pure prazepam.

REFERENCES

Bepko, F., Lowe, E., and Waxman, B. (1965). Relief of the emotional factor in labor with parenterally administered diazepam. *Obstet. Gynecol.*, **26**, 852.

Bowman, W. C., Rand, M. J., and West, G. B. (1968). *Textbook of Pharmacology*, 2nd edn. p. 272. Oxford & Edinburgh: Blackwell Scientific Publications.

Cavanagh, D., and Condo, C. S. (1964). Diazepam—a pilot study of drug concentrations in maternal blood, amniotic fluid and cord blood. *Curr. Ther. Res.*, **6**, 122.

Cree, J. E., Meyer, J., and Hailey, D. M. (1973). Diazepam in labour: its metabolism and effect on the clinical condition and thermogenesis of the newborn. *Br. Med. J.*, **4**, 251.

De Silva, J. A. F., d'Arconte, L., and Kaplan, J. (1964). The determination of blood levels and the placental transfer of diazepam in humans. *Curr. Ther. Res.*, **6**, 115.

Erkkola, R., Kangas, L., and Pekkarinen, A. (1973). The transfer of diazepam across the placenta during labour. *Acta Obstet. Gynaecol. Scand.*, **52**, 167.

—— Kanto, J., and Sellman, R. (1974). Perinatal metabolism of diazepam. *Br. Med. J.*, **3**, 472.

Flowers, C. E., Rudolph, A. J., and Desmond, M. (1969). Diazepam as an adjunct in obstetrical analgesia. *Obstet. Gynecol.*, **34**, 68.

Gamble, J. A. S., Assaf, R. A. E., Mackay, J. S., Kennedy, M. S., and Howard, P. J. (1975). Estimation of plasma diazepam. *Anaesthesia*, **30**, 159.

—— Moore, J., Lamki, H., and Howard, P. J. (1977). A study of plasma diazepam levels in mother and infant. *Br. J. Obstet. Gynaecol.*, **84**, 588.

Idanpaan-Heikkila, J. E., Jouppila, P. I., Poulakka, J. O., and Vorne, M. S. (1971). Placental transfer and fetal metabolism of diazepam in early human pregnancy. *Am. J. Obstet. Gynecol.*, **109**, 1011.

Joyce, D. N., and Kenyon, V. G. (1972). The use of diazepam and hydrallazine in the treatment of severe pre-eclampsia, *J. Obstet. Gynaecol. Br. Commonw.*, **79**, 250.

Lippold, O. C. J., and Winton, F. R. (1968). Human Physiology, 6th edn, p. 76. London: J. A. Churchill Ltd.

McAllister, C. B. (1977). A method for the quantitative collection of residues. *Ir. J. Med. Sci.*, **146**, 310.

—— (1978). The use of internal standards in the estimation of diazepam in plasma. *J. Chromatogr.*, **151**, 62.

McCarthy, G. T., O'Connell, B., and Robinson, A. E. (1973). Blood levels of diazepam in infants of two mothers given large doses of diazepam during labour. *J. Obstet. Gynaecol. Br. Commonw.*, **80**, 349.

Mandelli, M., Morselli, P. L., Nordio, S., Principi, N., Sernini, F., and Tognoni, G. (1975). Placental transfer of diazepam and its disposition in the newborn. *Clin. Pharmacol. Ther.*, **17**, 564.

Moore, R. G., and McBride, W. G. (1978). The disposition kinetics of diazepam in pregnant women at parturition. *Eur. J. Clin. Pharmacol.*, **13**, 275.

Mundow, L. S., and Long, S. V. (1974). The amnesic value of diazepam at forceps delivery. *Ir. J. Med. Sci.*, **143**, 101.

Owen, J. R., Irani, S. F., and Blair, A. N. (1972). Effect of diazepam administered to mothers during labour on temperature regulation of neonate. *Arch. Dis. Child.*, **47**, 107.

Rowlatt, R. J. (1978). Effect of maternal diazepam on the newborn. *Br. Med. J.*, **1**, 985.

Scher, J., Hailey, D. M., and Beard, R. W. (1972). The effects of diazepam on the foetus. *J. Obstet. Gynaecol. Br. Commonw.*, **79**, 635.

Shannon, R. W., Fraser, G. P., Aitken, R. G., and Harper, J. R. (1972). Diazepam in pre-eclamptic toxaemia with special reference to its effect on the newborn infant. *Br. J. Clin. Pract.*, **26**, 271.

Woods, D. L., and Malan, A. F. (1978). Side-effects of maternal diazepam on the newborn infant. *S.A. Med. J.*, **54**, 636.

Zingales, I. A. (1973). Diazepam metabolism during chronic medication: unbound fraction in plasma, erythrocytes and urine. *J. Chromatogr.*, **75**, 55.

TRANSFERT PLACENTAIRE ET EFFETS NATALS DU DIAZEPAM ADMINISTRE A DES FEMMES IMMEDIATEMENT AVANT L'ACCOUCHEMENT

RESUME

On a administré 10 mg de diazépam par voie intraveineuse à 23 femmes (groupe d'essai) juste avant leur accouchement. On a analysé le sang du cordon ombilical pour y rechercher le diazépam et on a comparé le bon état physique des nouveaux-nés du groupe d'essai à celui d'un groupe témoin approprié ($n=32$) en se basant sur l'analyse de covariance. Le diazépam a été décelé dans le sang des nouveaux-nés 30 s environ après son administration à la mère. On n'a décelé aucune différence importante dans le bon état physique des nouveaux-nés des deux groupes. On a par contre trouvé une relation inverse très significative entre la température rectale du nouveau-né et la concentration de diazépam dans le sang du cordon ombilical.

PLAZENTAÜBERTRAGUNG UND NEONATALE WIRKUNGEN VON DIAZEPAM BEI VERABREICHUNG AN FRAUEN KNAPP VOR DER GEBURT

ZUSAMMENFASSUNG

Zehn mg Diazepam wurden intravenös an 23 Patientinnen (Testgruppe) knapp vor der Geburt verabreicht. Das Nabelschnurblut wurde auf Diazepam untersucht, und das Wohlbefinden der Neugeborenen in der Testgruppe wurde mit dem in einer Kontrollgruppe (32 Patientinnen) mittels Kovarianzanalyse verglichen. Diazepam wurde im neonatalen Blut etwa 0,5 minuten nach Verabreichung an die Mutter entdeckt. Zwischen den beiden Gruppen gab es keine deutlichen Unterschiede im Wohlbefinden der Neugeborenen. Man fand jedoch ein sehr bedeutsames umgekehrtes Verhältnis zwischen der Analtemperatur des Neugeborenen und der Diazepamkonzentration im Nabelschnurblut.

TRANSFERENCIA DE PLACENTA Y EFECTOS NATALES DEL DIAZEPAM ADMINISTRADO A MUJERES JUSTO ANTES DEL PARTO

SUMMARIO

Se administraron 10 mg i.v. de diazepam a 23 pacientes (grupo prueba) justo antes del parto. Se analizó la sangre del cordón umbilical respecto del diazepam et se hizo una comparación del estado de los neonatos del grupo prueba y de un grupo control apropiado ($n=32$) por medio del análisis de covariación. Se encontró diazepam en la sangre del neonato alrededor de 0,5 min después de su administración a la madre. No hubo diferencias significativas en el estado de los neonatos de ambos grupos. Sin embargo, se observó una relación invertida muy significativa entre la temperatura rectal del recién nacido y la concentración de diazepam en la sangre del cordón umbilical.

Br. J. Anaesth. (1980), **52**, 429

COMPARISON OF THREE BENZODIAZEPINES FOR ORAL PREMEDICATION IN MINOR GYNAECOLOGICAL SURGERY

C. G. MALE, Y. T. LIM, M. MALE, J. M. STEWART AND J. M. GIBBS

SUMMARY

Diazepam 10 and 20 mg, lorazepam 2.5 and 5.0 mg, flunitrazepam 1 and 2 mg, and a placebo, were compared in a randomized double-blind controlled trial as oral premedication for 210 patients undergoing minor gynaecological surgery. Flunitrazepam 1 mg and lorazepam 2.5 mg were superior to placebo ($P < 0.001$ and $P < 0.05$ respectively) in relieving patient anxiety when assessed by a trained observer 60 min after premedication. Flunitrazepam 1 mg also produced more drowsiness ($P < 0.01$) than the placebo. Comparisons of other low-dose benzodiazepine groups with the placebo, and of the large dose with the small dose of each drug revealed no significant changes in anxiolysis or drowsiness. Dizziness and prolonged drowsiness were not apparent with low-dose flunitrazepam. The data suggests that flunitrazepam 1 mg offers advantages over placebo, diazepam 10 mg and lorazepam 2.5 mg for routine oral premedication in minor gynaecological surgery.

Reduction of fear and anxiety before anaesthesia and operation remains the prime reason for patient premedication (Atkinson, Rushman and Lee, 1977). Although a preoperative visit by the anaesthetist has been shown to lessen anxiety in surgical patients (Leigh, Walker and Janaganathan, 1977), medication before operation is widely used to allay patient fears over which the anaesthetist has less influence (Norris and Baird, 1967).

The benzodiazepine drugs diazepam, lorazepam and flunitrazepam are recognized anxiolytics. Oral preparations have have been compared for relative amnesic action (McKay, Dundee and George, 1978) and the first two have been investigated for night sedation and the relief of anxiety before operation (Paymaster, 1973; Wilson, 1973). Our double-blind controlled trial was designed to identify the relative potency of oral flunitrazepam and to compare its suitability for premedication with diazepam and lorazepam in patients undergoing minor gynaecological surgery.

METHODS

Female Caucasian patients admitted to four gynaecological wards for dilatation and curettage, and not in pain, were studied. The age range was 15–60 yr; weight 40.0–79.9 kg inclusive, ASA class I or II and the haemoglobin concentration greater than 10 g dl^{-1}. The Ethics Committee of the hospital approved the study and an anaesthetist sought informed verbal consent from the patient.

Patient height and body weight were recorded with current medication including overnight sedation, smoking habits and the state of any pregnancy (for example incomplete or therapeutic abortion).

The patient was assessed by a trained observer who gave scores for drowsiness (0–3), apprehension (0–3) and excitement (0–2) after Dundee, Moore and Nicholl (1962). Dizziness (0–2), emesis (0–3) and headache (0–2) were graded by questioning the patient. Rather than produce a single figure for all desired or undesired effects, we scored each aspect in an attempt to improve the discrimination between the effects of individual drugs.

As a self-rating score of anxiety, we asked the patient to choose from 11 anxiety-present and 10 anxiety-absent words, those adjectives which best described how the patient was feeling at that moment (Wassenaar et al., 1977). These were displayed in large print on cards (195 × 75 mm).

An Eysenck personality inventory (Form A) was completed by the patient to evaluate aspects of personality that might influence the success of drug

---

CHRISTOPHER G. MALE,* M.B., CH.B., F.F.A.R.C.S., F.F.A.R.A.C.S.; YONG, T. LIM, M.B., B.S.; MARION MALE,* S.R.N.; JOANNA M. STEWART, M.SC.; JOHN M. GIBBS, M.D., F.F.A.R.C.S., F.F.A.R.A.C.S.; Department of Anaesthesia, Christchurch Clinical School of Medicine, University of Otago, New Zealand.

* Reprint requests and correspondence to C. G. M. (present address): Department of Postgraduate Medicine, University of Keele, North Staffordshire Medical Institute, Hartshill Road, Hartshill, Stoke-on-Trent ST4 7NY.

0007-0912/80/040429-08 $01.00

© Macmillan Journals Ltd 1980

therapy. This provided scores for "neuroticism", "extroversion" and "lie" tendency (Eysenck and Eysenck, 1964).

Thirty doses each of diazepam 10 and 20 mg, lorazepam 2.5 and 5.0 mg and flunitrazepam 1 and 2 mg were prepared in paired identical capsules, using lactose as the placebo. This provided oral premedication for 210 patients in seven groups. Randomization was achieved by removing numbered cards from a bag. The contents of the two capsules in each numbered envelope were unknown to the trained observer, the anaesthetist and the patient. The code identifying the drug and dose with the patient remained unbroken until the end of the 6-month trial.

All patients were starved of food and fluid for at least 4 h before operation. Approximately 90 min before operation, the resting heart rate and the arterial pressure were recorded with the patient reclining at 45° in bed. Following the initial interview and questioning, the two capsules were dispensed by the trained observer, a registered nurse, for the patient to swallow whole in 10 ml of water. The patient was then left undisturbed in bed.

About 60 min after premedication, patient drowsiness, apprehension and excitement were again assessed by the observer, and then the patient selected from the 21 anxiety-related words as previously. The exact time of the assessment was noted with the resting heart rate and the arterial pressure. Dizziness, emesis, headache and heart rate change were recorded after questioning and observation.

Five picture cards (110 × 170 mm) of common objects from a series of 20 were shown to the patient and named by the observer for reinforcement. These were changed in cycle to prevent inter-patient contact distorting analysis of recall.

The patient was transported to the anaesthetic room on a trolley. Before induction, the anaesthetist recorded the effect of premedication as satisfactory or not by his own criteria. The nature of the surgical procedure, the anaesthetic technique employed and its duration were recorded. Although participating anaesthetists approved the double-blind controlled trial of benzodiazepine premedication, a standardized anaesthetic technique could not be formulated to cover both pregnant and non-pregnant patients.

On the morning following operation, the patient was assessed by the observer in respect of drowsiness, apprehension and excitement, and a self-rating score of anxiety obtained from the patient by adjective selection. An alternative form of the Eysenck personality inventory (Form B) was completed after operation by all patients except the first 33 studied, to whom it was unavailable. A score for amnesia was created by noting the recall of picture cards previously shown 1 h after premedication.

The statistical methods used were one-way analysis of variance, Kruskal–Wallis one-way analysis of variance followed by Dunn's test for multiple comparisons where appropriate (Dunn, 1964), Mann–Whitney *U* test, Chi-squared test, Wilcoxon matched-pairs signed-ranks test, Spearman's correlation coefficients and Fisher's discriminant analysis.

A rank analysis of covariance (Quade, 1967) was applied to those variables recorded both before and after premedication when investigating differences across the treatment groups. This has the effect of eliminating those differences across the treatment groups which might exist for the variable of interest before premedication, when looking at the differences after premedication. This was followed by Scheffe's method of multiple comparisons where appropriate.

RESULTS

The seven groups of 30 patients were comparable with respect to age, height, weight, ASA physical status, haemoglobin concentrations and state of pregnancy (table I). Similarly, the Eysenck personality inventories before operation (table II), patient self-rating scores for anxiety before premedication (table III) and the observer rating scores for drowsiness and apprehension before premedication (table IV) showed no significant differences across the seven groups. However, the observer rating score for excitement before premedication indicated that patients in the placebo group were more restless than those in the drug groups (table IV).

The first two trained observers withdrew after the first 32 and next 66 patients and the remaining 112 studies were completed by the third observer. This led to observer differences in the scoring across the groups of drowsiness ($P < 0.05$) and excitement ($P < 0.001$), but not apprehension. Such differences reduce the validity of drowsiness in assessing drug effect, and because of the placebo difference, excitement was excluded from further consideration.

Rank analysis of covariance of observer rating scores after premedication showed a significant difference for both drowsiness and apprehension amongst the seven treatment groups. Multiple comparison tests of placebo *v.* small doses and small doses *v.* large doses of each drug produced the

TABLE I. *Patient details*

		Diazepam		Lorazepam		Flunitrazepam	
	Placebo	10 mg	20 mg	2.5 mg	5.0 mg	1 mg	2 mg
No. of patients	30	30	30	30	30	30	30
Mean age (yr)	28	34	30	29	30	30	33
±SD	±9	±12	±12	±11	±13	±9	±10
Mean height (cm)	163	163	162	161	162	164	164
±SD	±6	±5	±7	±7	±6	±6	±6
Mean weight (kg)	58.3	60.2	62.1	59.9	59.8	58.6	61.3
±SD	±8.4	±9.4	±8.9	±9.7	±9.0	±6.6	±7.6
Mean haemoglobin (g dl^{-1})	13.39	13.34	13.35	13.40	13.34	13.21	13.66
±SD	±0.62	±0.98	±0.95	±1.08	±0.79	±1.09	±1.04
ASA physical status I/II	27/3	27/3	24/6	26/4	28/2	29/1	23/7
Non-pregnant	17	18	17	16	18	16	21
Spontaneous abortion	8	12	7	8	8	12	7
Therapeutic abortion	5	0	6	6	4	2	2

TABLE II. *Median Eysenck personality inventory scores*

		Diazepam		Lorazepam		Flunitrazepam	
	Placebo	10 mg	20 mg	2.5 mg	5.0 mg	1 mg	2 mg
No. of patients completed Form A	30	30	30	30	30	30	30
Before premedication							
Neuroticism	13.5	11.0	9.5	11.0	12.5	12.0	12.0
Extroversion	10.0	9.0	12.0	11.5	11.0	10.0	9.0
Lie	3.0	3.0	3.0	4.0	4.0	4.0	4.0
No. of patients completed Form B	25	24	27	24	23	27	26
After operation							
Neuroticism	14.0	13.5	14.0	12.5	15.0	13.0	14.0
Extroversion	13.0	14.0	13.0	15.0	13.0	14.0	14.0
Lie	2.0	2.0	2.5	1.0	2.0	1.5	2.0

TABLE III. *Patient self-rating median scores for anxiety. † max.* 11, *score* 1 *if selected; * max.* 10, *score* 1 *if not selected*

		Diazepam		Lorazepam		Flunitrazepam	
	Placebo	10 mg	20 mg	2.5 mg	5.0 mg	1 mg	2 mg
No. of patients	30	30	30	30	30	30	30
Before premedication							
Anxiety-present words†	2.5	2.0	2.0	1.0	3.0	2.0	1.0
Anxiety-absent words*	3.5	3.0	4.0	4.0	2.5	4.5	3.0
After premedication							
Anxiety-present words†	1.0	0.0	0.0	0.0	1.0	0.0	0.0
Anxiety-absent words*	4.5	2.0	2.0	4.0	2.5	3.0	2.0
After operation							
Anxiety-present words†	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Anxiety-absent words*	2.0	1.0	1.0	1.0	1.5	2.0	1.0

TABLE IV. *Observer rating median scores. Scoring system: drowsiness—good = 3, fair = 2, slight = 1, none = 0; apprehension—absent = 3, slight = 2, moderate = 1, marked = 0; excitement—nil = 2, slight = 1, marked = 0*

		Diazepam		Lorazepam		Flunitrazepam	
	Placebo	10 mg	20 mg	2.5 mg	5.0 mg	1 mg	2 mg
No. of patients	30	30	30	30	30	30	30
Before premedication							
Drowsiness	0.2	0.4	0.2	0.2	0.2	0.3	0.3
Apprehension	2.1	2.4	2.1	2.5	2.5	2.2	2.6
Excitement	1.6	1.9	1.9	1.9	1.8	1.9	2.0
After premedication (60 min)							
Drowsiness	1.0	1.7	2.1	1.6	2.6	2.5	2.9
Apprehension	2.4	2.8	2.9	2.9	3.0	2.9	3.0
Excitement	1.7	1.9	1.9	1.9	2.0	2.0	2.0
After operation (24 h)							
Drowsiness	0.2	0.2	0.4	0.5	0.8	0.2	0.2
Apprehension	2.7	2.9	2.9	2.8	2.7	2.9	2.9
Excitement	1.8	1.8	1.6	1.8	1.9	1.7	1.7

following results. Flunitrazepam 1 mg and lorazepam 2.5 mg induced significantly greater drowsiness than the placebo ($P<0.01$ and $P<0.05$ respectively), but doubling the dose of all three benzodiazepine failed to increase the drowsiness significantly. Only flunitrazepam 1 mg achieved significant relief of apprehension ($P<0.01$) when compared with the placebo. Again, doubling the dose of diazepam, lorazepam and flunitrazepam failed to relieve apprehension further.

For the self-rating scores of anxiety, a rank analysis of covariance was performed This showed no significant difference between the treatments for the number of anxiety-present words chosen, but the difference was significant ($P<0.05$) for the number of anxiety-absent words. The correlation coefficient between the observer rating score of apprehension and the patient self-rating score of anxiety (formed by the addition of the number of anxiety-absent and anxiety-present words chosen) before premedication was 0.51 and after premedication 0.30. Although highly significantly different from zero the coefficients are not very great.

An attempt was made to explain why some patients received little relief of apprehension or failed to become drowsy after receiving the active drug. A Fisher's discriminant analysis of the data for age, weight, haemoglobin, smoking habits, personality, patient's anxiety assessment, preoperative apprehension and time of assessment after premedication showed a tendency for those not gaining relief from apprehension to have been assessed earlier after premedication, and to have been slightly more apprehensive before premedication than others. However, these two factors did not explain the failure to relieve anxiety satisfactorily, therefore other unknown factors were operating. None of the above variables could account for the failure to become drowsy.

The anaesthetists distinguished a significant difference ($P<0.05$) in the drug response across the groups. This was mainly caused by describing the premedication as satisfactory in more cases receiving lorazepam 5 mg and flunitrazepam 2 mg and fewer cases given the placebo (table V).

TABLE V. *The anaesthetist's comment on the premedication*

		Diazepam		Lorazepam		Flunitrazepam	
	Placebo	10 mg	20 mg	2.5 mg	5.0 mg	1 mg	2 mg
Satisfactory	17	22	22	23	27	24	28
Unsatisfactory	13	8	8	7	3	6	2
Total no. of patients	30	30	30	30	30	30	30

Analysis of covariance on the toxic effects of dizziness and emesis after premedication revealed no significant differences. There was also no difference in heart rate change among the treatment groups (table VI). The dizziness was unrelated to decreases in systolic aterial pressure which were never unacceptably large. Patients in the placebo group were shown to have a greater severity of headache compared with those receiving the benzodiazepines ($P<0.01$).

TABLE VI. *Median rating scores for undesired effects. Scoring system: dizziness—marked = 2, slight = 1, none = 0; emesis—vomiting = 3, marked nausea = 2, slight nausea = 1, none = 0; headache—severe = 2, slight = 1, none = 0; heart rate change—increase ≥ 21 beat min^{-1} = 3, increase 1–20 beat min^{-1} = 2, no change = 1, decrease = 0*

	Placebo	Diazepam		Lorazepam		Flunitrazepam	
		10 mg	20 mg	2.5 mg	5.0 mg	1 mg	2 mg
Before premedication							
Dizziness	0.1	0.0	0.1	0.0	0.1	0.1	0.0
Emesis	0.2	0.1	0.2	0.1	0.1	0.0	0.1
Headache	0.5	0.4	0.3	0.2	0.2	0.2	0.4
After premedication							
Dizziness	0.1	0.1	0.1	0.0	0.1	0.1	0.1
Emesis	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Headache	0.7	0.2	0.1	0.1	0.2	0.2	0.2
Heart rate increase	1.1	1.1	1.5	1.4	1.8	1.2	0.7

Postoperative assessment 24 h after premedication confirmed significantly different recall of the picture cards shown 1 h after premedication between the seven groups ($P < 0.001$) (table VII). A comparison of the alternative form (B) with the original form (A) of the Eysenck personality inventory showed significant ($P < 0.001$) increases in "neurosis" and "extroversion" scores and a decrease ($P < 0.001$) in the "lie" score after operation.

TABLE VII. *Patient recall of picture cards shown 60 min after premedication*

	Placebo	Diazepam		Lorazepam		Flunitrazepam	
		10 mg	20 mg	2.5 mg	5.0 mg	1 mg	2 mg
No. of patients	30	30	30	30	30	30	30
No. of cards recalled							
5	8	4	1	2	0	1	1
4	6	9	1	3	0	2	1
3	8	3	5	6	6	1	0
2	6	5	8	2	3	8	2
1	1	5	4	6	4	8	0
0	1	4	11	11	17	10	26
Group total	101	80	44	50	28	40	13

The observer rating score for drowsiness after operation using the rank analysis of covariance produced a significant difference ($P < 0.01$) across the groups, but surprisingly the apprehension score was not significantly different (table IV).

Although the frequency and nature of complications after operation was influenced by the anaesthetic technique, most patients expressed a preference for oral rather than parenteral premedication. All patients had recovered sufficiently for discharge home from hospital the day after surgery but some remained for surgical reasons.

DISCUSSION

Our study supports the view that oral benzodiazepines offer useful sedation and anxiolysis as premedication for minor gynaecological surgery. Diazepam 10 mg failed to produce significantly greater drowsiness than placebo when given 1 h before assessment. Lorazepam 2.5 mg and flunitrazepam 1 mg gave a significant increase in drowsiness compared with the placebo. These observations match the clinical use of diazepam for daytime anxiolysis without drowsiness and that of nitrazepam for night sedation. Lorazepam is the ortho-chloro-phenyl derivative of the main metabolite of diazepam, desmethyldiazepam. Like diazepam, its use for daytime relief of apprehension has been more popular than as a night hypnotic. All will induce sleep at greater doses, although doubling the small dose in our study did not increase drowsiness significantly within each drug grouping.

Unfortunately, a drowsy state does not necessarily mean that apprehension has been abolished (Egbert et al., 1963; Morrison, Clarke and Dundee, 1970). Relief of apprehension must be sought from premedication to reduce excessive hormonal and circulatory response which might antagonize the safe induction with the minimal effective dose of anaesthetic agent. We attempted to assess patient anxiety before premedication by two different measures. The patient self-rating score of anxiety was derived from the Multiple Affect Adjective Check List (MAACL) described by Zuckerman (1960) but only 21 anxiety-related words out of the original list bearing 132 words were used, and appropriate key words previously used for the assessment of depression and hostility (Wassenaar et al., 1977) were omitted. Patient illiteracy and the short time available for assessment necessitated these modifications. Assessment of apprehension was also gained through use of a four-point observer rating scale. Correlation between the patient self-rating score and the observer rating score for anxiety in our study was poor unlike the findings of others (Wassenaar et al., 1977). This was probably because the sensitivity of the former was reduced by extracting the 21 anxiety-related words out of the 132 word list. Also, fewer of the 11 anxiety-present words were selected than those of the 10 anxiety-present words omitted by the patient (table III). An analogue line scoring system (Wilson, 1969) might have been a more sensitive subjective method of assessing apprehension. The observer four-point rating score of anxiety was used for statistical analysis of data because of its widespread application previously (Morrison, Hill and Dundee, 1968).

We were unable to explain why some patients received little relief of their apprehension from the active drugs although assessment of the premedication before the 60-min interval had elapsed and increased apprehension before premedication were factors more frequently found in this group. Surprisingly, those who requested night sedation with nitrazepam 10 mg before operation failed to get much relief from the benzodiazepine premedication, implying tolerance or minimal residual effect which is contrary to previous experience (Malpas et al., 1970).

Amnesia for unpleasant aspects of the perioperative period is a useful ingredient of premedication and the benzodiazepine group of drugs share this effect. Lack of recall of picture cards does not necessarily mean that the patient will not remember events such as the journey to the operating theatre, and induction of anaesthesia, but recall of the long time spent lying on an uncomfortable theatre trolley may be obtunded. We demonstrated a differing amount of recall of five cards shown 1 h after premedication across the one placebo and six drug groups (table VII). The relative amnesic actions and duration of effect have been described for i.v. diazepam, lorazepam and flunitrazepam (George and Dundee, 1977).

The frequency of observed toxic effects from benzodiazepine premedication is small (table VI) and there was no significant difference across the drug groups except for headache ($P<0.01$). When examining the difference in median values after and before premedication, the placebo group recorded a higher score for headache whereas none of the drug groups showed an increase. Whether precipitated by fluid deprivation or emotional tension, benzodiazepine premedication seems to reduce the frequency and severity of headache, although these drugs have no analgesic properties.

Dizziness is a recognized side-effect of larger doses of all benzodiazepine drugs, but as there was no significant difference amongst the treatment groups this was not shown in our study. Blurred vision occasionally accompanied dizziness when moderate or severe.

Despite the number of anaesthetists judging the premedication immediately before induction, by various personal criteria, there was a significant difference in satisfactory comments across the drug groups (table V). This implied that benzodiazepine premedication probably did not interact adversely with the chosen anaesthetic techniques. It is interesting that the placebo was approved as a satisfactory premedication in 57% of those who received it.

The influence of different trained observers on the rating score of drowsiness and excitement was quite marked. This observation contrasts with the findings of a previous study using the same observer assessment scheme (Morrison, Hill and Dundee, 1968). However, in that study a single score of efficacy or desired effect was generated from combined assessment of sedation, freedom from apprehension and restlessness. We sought to distinguish each aspect and this discrimination led to differences in observer rating scores for excitement particularly, and somewhat less for drowsiness.

Lorazepam has an elimination half-life of 12 h, but has no active metabolites (Elliott, 1976). Diazepam and its major active metabolite, desmethyldiazepam, have elimination half-lives of more than 24 h. Changes in serum flunitrazepam concentrations after i.v. injection of doses comparable to those in our study follow the same pattern as diazepam, but with 7-aminoflunitrazepam as the main metabolite (Korttila and Linnoila, 1974). Drowsiness and tiredness with deterioration of co-ordinating skills were demonstrable for up to 10 h after i.v. flunitrazepam and behavioural tests were impaired for 12 h after oral flunitrazepam (Bond and Lader, 1975). The fact that it was a young female patient population which we studied may explain the disparity between these findings and our observations. A detailed study of the postoperative recovery period after flunitrazepam premedication and standardized anaesthetic technique seems to be indicated.

The significant changes in "neuroticism", "extroversion" and "lie" scores from before to after operation might be the result of the difference in content of alternative forms A and B, or the developing relationship of the observer and patient. It was disappointing to find that personality characteristics could not predict who might not gain relief of apprehension from standard benzodiazepine premedication. A strong positive correlation has been noted between the neuroticism score and vital capacity impairment with chest complications in female patients undergoing elective cholecystectomy (Dalrymple, Parbrook and Steel, 1973). The lie score showed a significant correlation with the patient's subjective pain assessment in the same study, but not with the response of male patients to i.v. methadone or inhaled nitrous oxide for analgesia after gastric surgery (Dalrymple and Parbrook, 1976).

The development of the benzodiazepine group of drugs has given the anaesthetists a variety of interesting agents with different characteristics. If relief of apprehension and drowsiness within 1 h of oral premedication are desirable for patients undergoing minor gynaecological procedures, flunitrazepam 1 mg offers advantages over the placebo, diazepam and lorazepam. However, the improved efficacy is not accompanied by a significant increase in undesired effects.

ACKNOWLEDGEMENTS

The authors would like to record their gratitude for the kind co-operation of the nursing staff, surgeons and anaesthetists at Christchurch Women's Hospital, for the financial support of Roche Products (New Zealand) Ltd and the excellent secretarial assistance of Miss Joan Larsen.

REFERENCES

Atkinson, R. S., Rushman, G. B., and Lee, J. A. (1977). *A Synopsis of Anaesthesia*, 8th edn, p. 108. Bristol: John Wright.

Bond, A. J., and Lader, M. H. (1975). Residual effects of flunitrazepam. *Br. J. Clin. Pharmacol.*, **2**, 143.

Dalrymple, D. G., and Parbrook, G. D. (1976). Personality assessment and postoperative analgesia. A study in 40 male patients undergoing elective gastric surgery. *Br. J. Anaesth.*, **48**, 593.

—— —— Steel, D. F. (1973). Factors predisposing to postoperative pain and pulmonary complications. A study of 50 female patients undergoing elective cholecystectomy. *Br. J. Anaesth.*, **45**, 589.

Dundee, J. W., Moore, J., and Nicholl, R. M. (1962). Studies of drugs given before anaesthesia. I: A method of preoperative assessment. *Br. J. Anaesth.*, **34**, 458.

Dunn, O. J. (1964). Multiple comparisons using rank sums. *Technometrics*, **6**, 241.

Egbert, L. D., Battit, G. E., Turndorf, H., and Beecher, H. K. (1963). The value of the preoperative visit by an anaesthetist. *J.A.M.A.*, **185**, 553.

Elliott, H. W. (1976). Metabolism of lorazepam. *Br. J. Anaesth.*, **48**, 1017.

Eysenck, H. J., and Eysenck, S. B. G. (1964). *The Eysenck Personality Inventory*. London: University of London Press.

George, K. A., and Dundee, J. W. (1977). Relative amnesic actions of diazepam, flunitrazepam and lorazepam in man. *Br. J. Clin. Pharmacol.*, **4**, 45.

Korttila, K., and Linnoila, M. (1974). Skills related to driving after intravenous diazepam, flunitrazepam or droperidol. *Br. J. Anaesth.*, **46**, 961.

Leigh, J. M., Walker, J., and Janaganathan, J. (1977). Effect of preoperative anaesthetic visit on anxiety. *Br. Med. J.*, **2**, 987.

McKay, A. C., Dundee, J. W., and George, K. A. (1978). The amnesic effects of orally administered benzodiazepines. *Br. J. Anaesth.*, **50**, 1080P.

Malpas, A., Rowan, A. J., Joyce, C. R. B., and Scott, D. F. (1970). Persistent behavioural and electroencephalographic changes after single doses of nitrazepam and amylobarbitone sodium. *Br. Med. J.*, **2**, 762.

Morrison, J. D., Clarke, R. S. J., and Dundee, J. W. (1970). Studies of drugs given before anaesthesia. XXI: droperidol. *Br. J. Anaesth.*, **42**, 730.

—— Hill, G. B., and Dundee, J. W. (1968). Studies of drugs given before anaesthesia. XV: Evaluation of the method of study after 10 000 observations. *Br. J. Anaesth.*, **40**, 890.

Norris, W., and Baird, W. L. M. (1967). Preoperative anxiety: a study of the incidence and aetiology. *Br. J. Anaesth.*, **39**, 503.

Paymaster, N. J. (1973). Lorazepam (WY 4036) as a preoperative medication. *Anaesthesia*, **28**, 521.

Quade, D. (1967). Rank analysis of covariance. *J. Am. Stat. Assoc.*, **62**, 1187.

Wassenaar, W., Lancee, W. J., Galloon, S., and Gale, G. D. (1977). The measurement of anxiety in the presurgical patient. *Br. J. Anaesth.*, **49**, 605.

Wilson, J. (1969). A preliminary evaluation of analogue scoring in sedation. *Br. J. Anaesth.*, **41**, 789.

—— (1973). Lorazepam as a premedicant for general anaesthesia. *Curr. Med. Res. Opin.*, **1**, 308.

Zuckerman, M. (1960). The development of an affect adjective check list for the measurement of anxiety. *J. Consult. Clin. Psychol.*, **24**, 457.

COMPARAISON DE TROIS BENZODIAZEPINES POUR ADMINISTRATION PAR VOIE BUCCALE EN TANT QUE PREMEDICATION POUR LES INTERVENTIONS GYNECOLOGIQUES MINEURES

RESUME

On a comparé, au cours d'une étude contrôlée à double inconnue effectuée au hasard, les effets de diazépam, à raison de 10 et 20 mg, du lorazépam, à raison de 2,5 et 5 mg, du flunitrazépam à raison de 1 et de 2 mg, ainsi que d'un

placebo, administré par voie buccale en tant que prémédication à 210 femmes devant subir des interventions chirurgicales gynécologiques mineures. Le flunitrazépam à raison de 1 mg et le lorazépam à raison de 2,5 mg ont été meilleurs que le placebo ($P < 0{,}001$ et $P < 0{,}05$ respectivement) pour soulager l'anxiété de la malade, lorsque cette anxiété a été evaluée par un observateur entrainé 60 mn après l'administration de la prémédication. Le flunitrazépam à raison de 1 mg a aussi produit davantage de somnolence diurne que le placebo ($P < 0{,}01$). Les comparaisons des autres groupes de benzodiazépine à faible dose avec le placebo, et de la forte dose avec la faible dose de chaque produit n'ont indiqué aucun changement significatif dans l'anxiolyse ou la somnolence diurne. On n'a remarqué aucun malaise ou aucune somnolence avec le flunitrazépam administré à faible dose. Les données laissent penser que le flunitrazépam à raison de 1 mg présente des avantages par rapport au placebo, au diazépam à raison de 10 mg ou au lorazépam à raison de 2,5 mg pour l'administration routinière par voie buccale, lors des interventions chirurgicales gynécologiques mineures.

VERGLEICH DREIER BENZODIAZEPINE FÜR ORALE VORBEHANDLUNG FÜR KLEINERE GYNÄKOLOGISCHE EINGRIFFE

ZUSAMMENFASSUNG

Diazepam 10 und 20 mg, Lorazepam 2,5 und 5,0 mg, Flunitrazepam 1 und 2 mg sowie ein Plazebo wurden in einem willkurlichen, doppelblind-kontrolliertem Versuch als orales Vorbehandlungsmittel bei 210 Patienttinnen getestet, die sich kleineren gynäkologischen Eingriffen unterzogen. Flunitrazepam 1 mg und Lorazepam 2,5 mg waren dem Plazebo überlegen ($P < 0{,}001$ bezw. $P < 0{,}05$), was den Beruhigungseffekt betraf, der von einem geschulten Boebachter 60 Minuten nach Verabreichung beurteilt wurde. Flunitrazepam 1 mg bewirkte auch mehr Schläfrigkeit als das Plazebo. Vergleiche anderer Benzodiazepine in niedrigen Dosen mit dem Plazebo, und Vergleiche zwischen grossen und kleinen Dosen der jeweiligen Droge zeigten keine wesentlichen Änderungen bei Anxiolyse oder Scläfrigkeit. Schwindel uod verlängerte Schläfrigkeit zeigten sich bei niedrig dnsiertem Flunitrazepam nicht. Diese Daten zeigen, dass Flunitrazepam 1 mg, vorteilhaft ist gegenüber Plazebo, Diazepam 10 mg und Lorazepam 2,5 mg wenn es um routinemässige orale Vorbehandlung für kleinere gynäkologische Eingriffe geht.

COMPARACION DE TRES BENZODIAZEPINAS PARA PREMEDICACION ORAL EN CIRUJIA GINECOLOGICA MENOR

SUMARIO

Se procedío a una comparación de 10 y 20 mg de diazepam, 2,5 y 5,0 mg de lorazepam, 1 y 2 mg de flunitrazepam y de un placebo en una prueba doble-ciega controlada al azar, como premedicación oral de 210 pacientes sometidas a operaciones quirúrgicas ginecológicas menores. Se comprobó que 1 mg de flunitrazepam y 2,5 mg de lorazepam daban mejores resultados que el placebo ($P < 0{,}001$ y $P < 0{,}05$, respectivamente) en aliviar la ansieded de las pacientes cuando los evaluaba un observador capacitado 60 min después de la premedicación. Con 1 mg de flunitrazepam se producía también mayor somnolencia que con el placebo ($P < 0{,}01$). No se registraron cambios significativos de la ansiólisis o de la somnolencia al realizar comparaciones de otros grupos de benzodiazepinas en dosis menores con el placebo, y de dosis mayores con dosis menores de cada substancia. No se manifestaron vértigos ni somnolencia prolongada con el flunitrazepam en dosis bajas. Estos datos hacen pensar que 1 mg de flunitrazepam es más ventajoso que el placebo, 10 mg de diazepam, y 2,5 mg de lorazepam para la premedicación oral corriente en operaciones quirúrgicas ginecológicas menores.

Br. J. Anaesth. (1980), **52**, 437

COMPARISON OF THE SUBJECTIVE EFFECTS AND PLASMA CONCENTRATIONS FOLLOWING ORAL AND I.M. ADMINISTRATION OF FLUNITRAZEPAM IN VOLUNTEERS

R. S. J. Clarke, J. W. Dundee, W. A. W. McGowan and P. J. Howard

SUMMARY

Flunitrazepam 0.5, 1.0 or 2.0 mg was given by the oral or i.m. routes to groups of volunteers and its effects compared. Plasma concentrations of the drug were estimated by gas–liquid chromatography, in a smaller number of the subjects. The most striking effect was sedation which increased with the dose, 2 mg producing deep sleep although the subjects could still be aroused. The effects of i.m. administration were apparent earlier and sometimes lasted longer than those following oral administration. Dizziness was less marked than sedation, but increased with the dose. There was pain on i.m. injection of flunitrazepam significantly more often than with isotonic saline. Plasma concentrations varied with dose and route and corresponded qualitatively with the subjective effects. The drug was still present in measurable quantities after 24 h even with the smallest dose.

Flunitrazepam, an alternative benzodiazepine to diazepam, has a potency of 10–20 times that of the longer established drug. Although flunitrazepam, when administered by the i.v. route, does not cause the same high frequency of local phlebitis and thrombosis as diazepam (Hegarty and Dundee, 1977) it has few advantages as an anaesthetic induction agent, being similar to diazepam as regards its delay in onset, variability of action and degree of hypotension produced (Stovner, Endresen and Osterud, 1973; Dundee et al., 1976; Clarke and Lyons, 1977). Both drugs produce some anterograde amnesia when given i.v., but the action of flunitrazepam is more prolonged (George and Dundee, 1977). However, it could replace diazepam as a narcotic during minor surgical procedures with or without local anaesthesia.

The place of flunitrazepam as a premedicant needs to be evaluated also, since diazepam is now well established in this field. Diazepam is absorbed more rapidly and reliably by mouth than following i.m. injection (Gamble, Dundee and Assaf, 1975); it is not known whether the same applies to flunitrazepam. This study was undertaken to determine the relationship between the effects of flunitrazepam in different doses and the concentration of the drug in the plasma. It was carried out in volunteers to ensure that no other drugs or anaesthetic agents were given over the ensuing 24 h and to enable cross-over estimations of plasma concentrations to be performed when the drug was given by either route.

METHODS

The subjects were healthy medical students taking part in a clinical pharmacology class. They were given information about the procedure in detail and agreed to take part. In each class of 10 to 12, approximately half acted as subjects and the remainder were observers. There was no selection of students except that those who needed to drive a car home were excluded.

Students received one of the following treatments: flunitrazepam 0.5 or 1.0 mg by mouth with saline i.m.; placebo by mouth with flunitrazepam 0.5 or 1.0 mg i.m., or placebo by mouth with saline 1 ml i.m. This gave five treatments (table I). Injections were into the vastus lateralis muscle. Neither subject nor observer knew which treatment had been given and the code was not broken until the end of each term, when findings were discussed with the class.

Subjects lay on a couch and the heart rate and arterial pressure (Riva Rocci) were recorded when supine and immediately after standing up. Three sets of control readings were taken before the drug was given. After the administration of the drug the four observations were repeated every 10 min for 1 h. The occurrence of side-effects such as sleepiness, dizziness, restlessness, pain at injection site and dryness of the mouth was noted every 10 min. Their severity was graded as slight or marked. The subjects were asked to note any of these side-effects at 6, 18 and 24 h after receiving the drug and report back

---

R. S. J. Clarke, M.D., PH.D., F.F.A.R.C.S.; J. W. Dundee M.D., PH.D., F.F.A.R.C.S., M.R.C.P.; W. A. W. McGowan, M.D., F.F.A.R.C.S.; P. J. Howard, F.S.A.L.T., F.I.S.T.; Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland.

0007-0912/80/040437-09 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Details of subjects in the various experimental groups*

Drugs received	No. of subjects	Average age (yr)	Average weight (kg)
Assessment			
Flunitrazepam 2 mg (i.m. and oral)	5	35	66
Flunitrazepam 1 mg oral (+i.m. placebo)	25	22	66
Flunitrazepam 1 mg i.m. (+oral placebo)	25	22	67
Flunitrazepam 0.5 mg oral (+i.m. placebo)	25	21	68
Flunitrazepam 0.5 mg i.m. (+oral placebo)	25	21	67
Placebo oral+i.m.	50	22	69
Assessment and plasma drug concns			
Flunitrazepam 2 mg (i.m. and oral)	5	35	66
Flunitrazepam 1 mg (i.m. and oral)	11	21	72
Flunitrazepam 0.5 mg (i.m. and oral)	11	21	68

with the completed forms on the next day. They could, of course, contact a senior member of the academic staff if there were any severe symptoms after the class.

Twenty-five students received each of the above treatments and these included 11 who were asked to volunteer for additional measurements of blood concentrations of flunitrazepam. An 18-gauge Medicut cannula was inserted into an antecubital vein and blood samples were withdrawn at 0, 15, 30, 45, 60 and 90 min as well as after 24 h. Each volunteer received flunitrazepam by one route and was asked to return on a further occasion, at least 1 week later, to receive the drug by the other route. The blood was transferred immediately into heparinized tubes and centrifuged within 1 h of sampling. The plasma was stored in non-heparinized bottles at −20 °C until the flunitrazepam concentration was estimated.

In a further small series blood concentrations and general effects were measured after flunitrazepam 2 mg. Only five volunteers were studied at this time and again a cross-over technique was employed. These subjects were all members of the departmental staff and studies were begun at 09.00 h to ensure recovery before night. They were not asked to stand up after receiving the drug until it was clear that they were able to do so.

The groups of subjects (table I) were broadly comparable with respect to age and weight, except that those receiving 2 mg were older.

Estimation of plasma flunitrazepam

The method of extraction in benzene is similar to that developed in this Department for the analysis of diazepam in plasma samples (Gamble et al., 1975). Estimation was by gas-liquid chromatography, as in the method of estimation of lorazepam (Howard et al., 1977), the only difference being the internal standard which in this case was lorazepam 150 ng ml^{-1}. In order to minimize possible day-to-day variation in extraction technique and standard preparation, all samples from each patient were analysed on one day. The results quoted are based on the average of duplicate estimations:

Column: 1.75 m × 5 mm borosilicate glass, packed with 3% OV17 on gas chrom Q, 80–100 mesh

Carrier gas: oxygen-free nitrogen (OFN) at a pressure of 350 kN m^{-2}

Injection temperature: 300 °C

Detector temperature: 300 °C

Column temperature: 240 °C

Under these conditions flunitrazepam eluted at 2.6 min and lorazepam at 2 min.

RESULTS

Sedation

Flunitrazepam, in all doses studied and by either route, led to significantly more sedation than the placebo between 30 min and 6 h (table II). It was particularly notable that few subjects receiving the inert preparation complained of drowsiness for more than 1 h (the duration of the class) while many who received the drug noticed its effect for the whole evening. There was a marked dose-related difference in action. Some of the individuals did not detect any symptoms with the 0.5-mg dose, whereas all went into a deep sleep with the 2.0-mg dose, although they were rousable on stimulation. In general there was marked variation in the effects of the drug from individual to individual.

The effects of the i.m. administration were apparent earlier and sometimes lasted longer than those of the same dose given by mouth (table II, fig. 1). This difference was significant with the two smaller doses at 10, 20 and 30 min. Although the numbers receiving 2 mg were small, there was little difference between the routes in onset or severity of sedation although it lasted longer in most subjects after the i.m. administration.

TABLE II. *Percentage frequency of sedation, dizziness and pain at injection site at certain times after placebo and three doses of flunitrazepam, given by the i.m. and oral routes. The two sets of findings for the placebo represent the same subjects who received both the saline injection and the placebo tablet.*
* *Indicates that the i.m. frequency is significantly greater than the oral* ($P < 0.05$)

		I.m.										Oral									
		0	10	20	30	40	50	60	6	18	24	0	10	20	30	40	50	60	6	18	24
	Symptoms							(min)	(h)									(min)	(h)		
Placebo	Sedation	0	0	12	16	22	26	22	8	4	4	0	0	12	16	22	26	22	8	4	4
	Dizziness	0	4	2	2	2	2	2	0	0	0	0	4	2	2	2	2	2	0	0	0
	Pain	0	14	4	4	4	2	2	4	4	4	0	14	4	4	4	2	2	4	4	4
Flunitrazepam 0.5 mg	Sedation	0	32*	68*	64*	72	68	52	52	8	0	0	0	12	36	48	64	56	48	8	0
	Dizziness	0	36*	56*	56*	60	48	44	4	0	0	0	4	16	28	52	36	28	8	0	0
	Pain	0	44	44	48	48	44	44	20	8	4	0	0	0	0	0	0	0	0	0	0
Flunitrazepam 1.0 mg	Sedation	0	68*	80*	88*	84	84	84	72	24*	4	0	4	28	56	68	76	76	64	4	8
	Dizziness	0	40*	52	48	64	60	44	20	4	0	0	8	32	56	52	60	68	24	0	0
	Pain	0	40	32	32	36	36	44	20	8	4	0	0	0	0	0	0	0	0	0	0
Flunitrazepam 2.0 mg	Sedation	0	40	80	100	100	100	100	100	0	0	0	40	100	100	100	100	100	40	20	0
	Dizziness	0	0	100	100	100	100	100	100	0	0	0	20	100	100	100	100	100	40	0	0
	Pain	0	100	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0	0	0

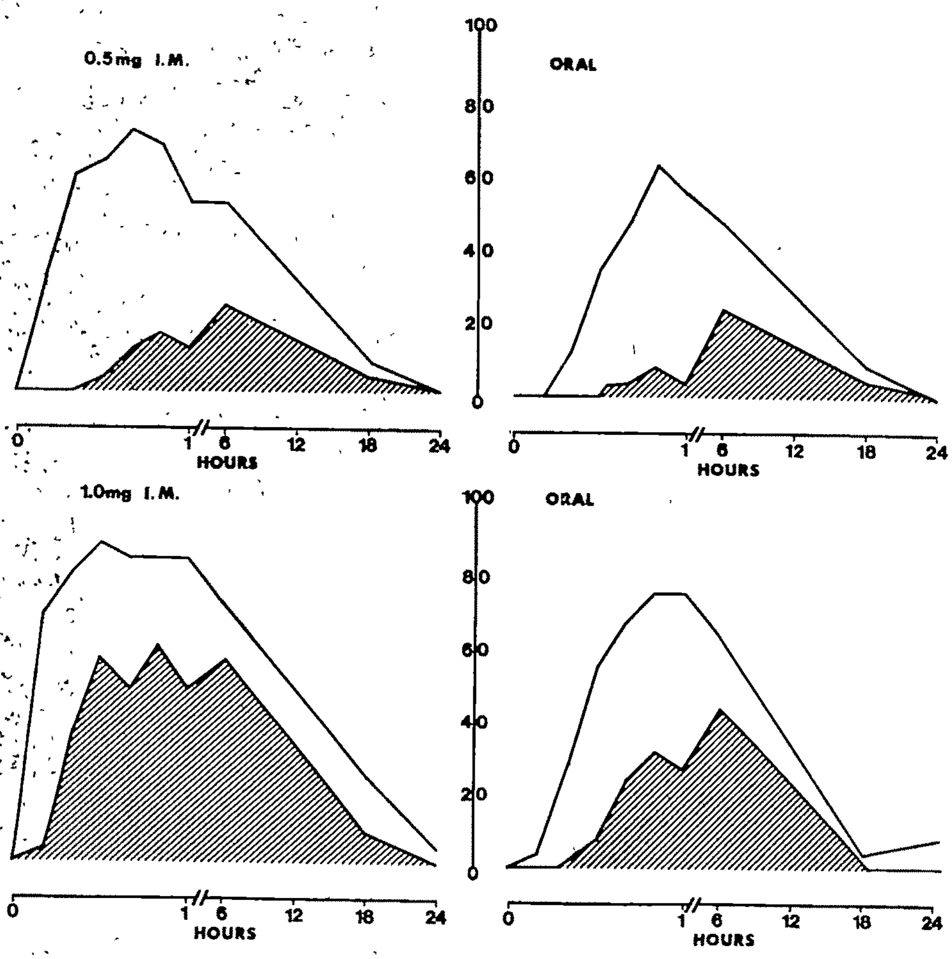


FIG. 1. Percentage (vertical axis) of subjects showing drowsiness (clear area) and severe drowsiness (hatched area) after flunitrazepam 0.5 or 1.0 mg. The lines show the mean of 25 subjects, each of whom received the drug either by the i.m. or by the oral route.

Dizziness

This was particularly apparent when the subjects stood up. It followed sedation closely in timing, although it was less frequent and less severe (table II; fig. 2). It was also more marked when flunitrazepam was given by the i.m. route, the difference again being significant with 0.5 mg at 10, 20 and 40 min after administration. With the 1.0-mg dose the difference was significant only at 10 min.

Pain at the site of injection

This occurred significantly more frequently with the flunitrazepam injections than with normal saline during the first 6 h after administration (table II). The frequency was similar with the 0.5- and 1.0-mg doses, but the high frequency with the 2.0-mg dose may have been related to the larger volume.

Other side-effects, such as muscle weakness, inability to concentrate and dryness of mouth were noted in the same proportion of subjects in drug and placebo groups.

Arterial pressure decreased significantly during the 1st hour with flunitrazepam and with the placebo, but there was no significant difference between the groups. The average decrease in mean arterial pressure, either supine or standing, did not exceed 5 mm Hg. The average heart rate decreased significantly in all groups (including placebo), the average being 5–7 beat min^{-1}.

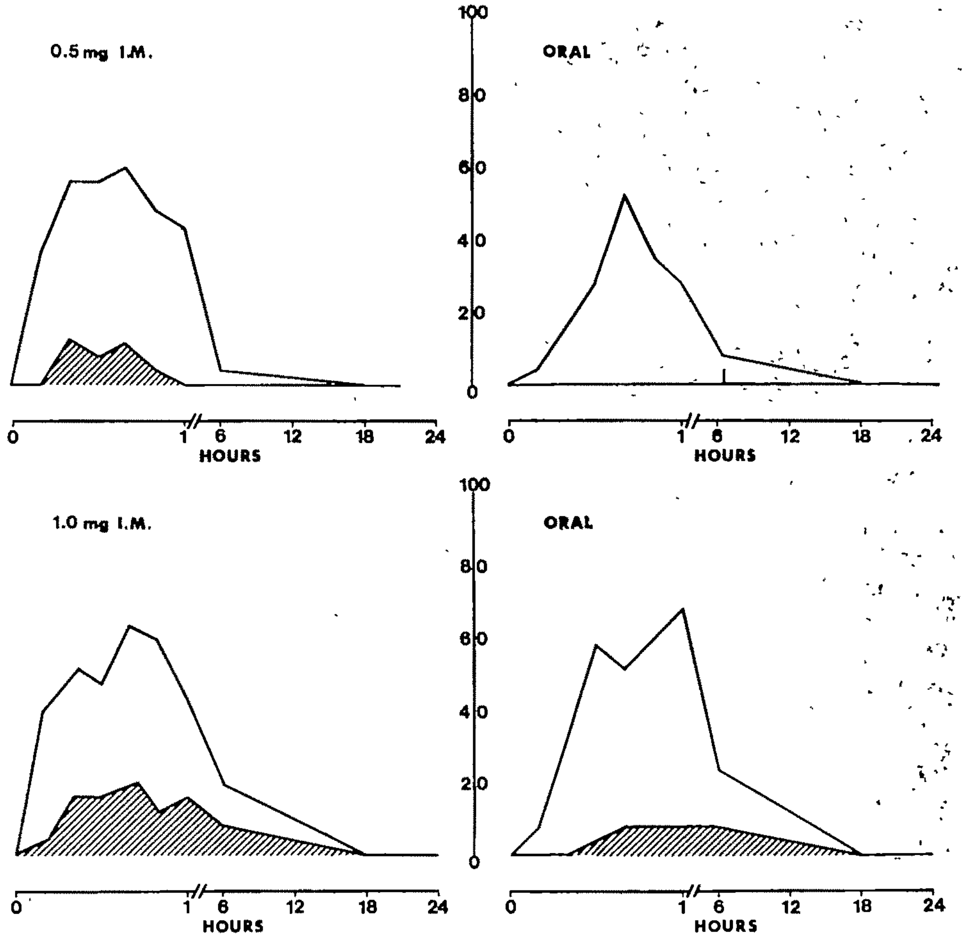


FIG. 2. Percentage (vertical axis) of subjects showing dizziness (clear area) and severe dizziness (hatched area) after flunitrazepam 0.5 or 1.0 mg. The lines show the mean of 25 subjects, each of whom received the drug either by the i.m. or by the oral route.

TABLE III. *Plasma concentrations of flunitrazepam (mean ± SEM) after three different doses of the drug given to the same subjects by two routes. * Indicates that the plasma concentration after i.m. administration is significantly greater than after administration by the oral route* ($P < 0.05$)

	I.m. route (ng ml^{-1})						Oral route (ng ml^{-1})					
	15 min	30 min	45 min	60 min	90 min	24 h	15 min	30 min	45 min	60 min	90 min	24 h
Flunitrazepam 0.5 mg												
Mean	3.52*	3.23*	2.75*	2.60	2.15	0.71	0.44	1.34	1.47	1.73	2.23	0.50
SEM	0.62	0.47	0.32	0.26	0.21	0.15	0.13	0.29	0.29	0.39	0.45	0.07
Flunitrazepam 1.0 mg												
Mean	2.27*	2.95*	3.25*	3.31*	2.75	0.95	0.67	1.62	1.95	2.13	2.50	0.85
SEM	0.56	0.52	0.55	0.43	0.36	0.11	0.21	0.30	0.37	0.29	0.32	0.15
Flunitrazepam 2.0 mg												
Mean	8.36	16.08	19.86	24.60	21.76*	2.96	12.26	14.36	14.74	14.76	13.84	3.92
SEM	3.16	6.34	3.84	4.49	3.43	0.63	9.95	5.02	2.14	1.76	2.31	0.39

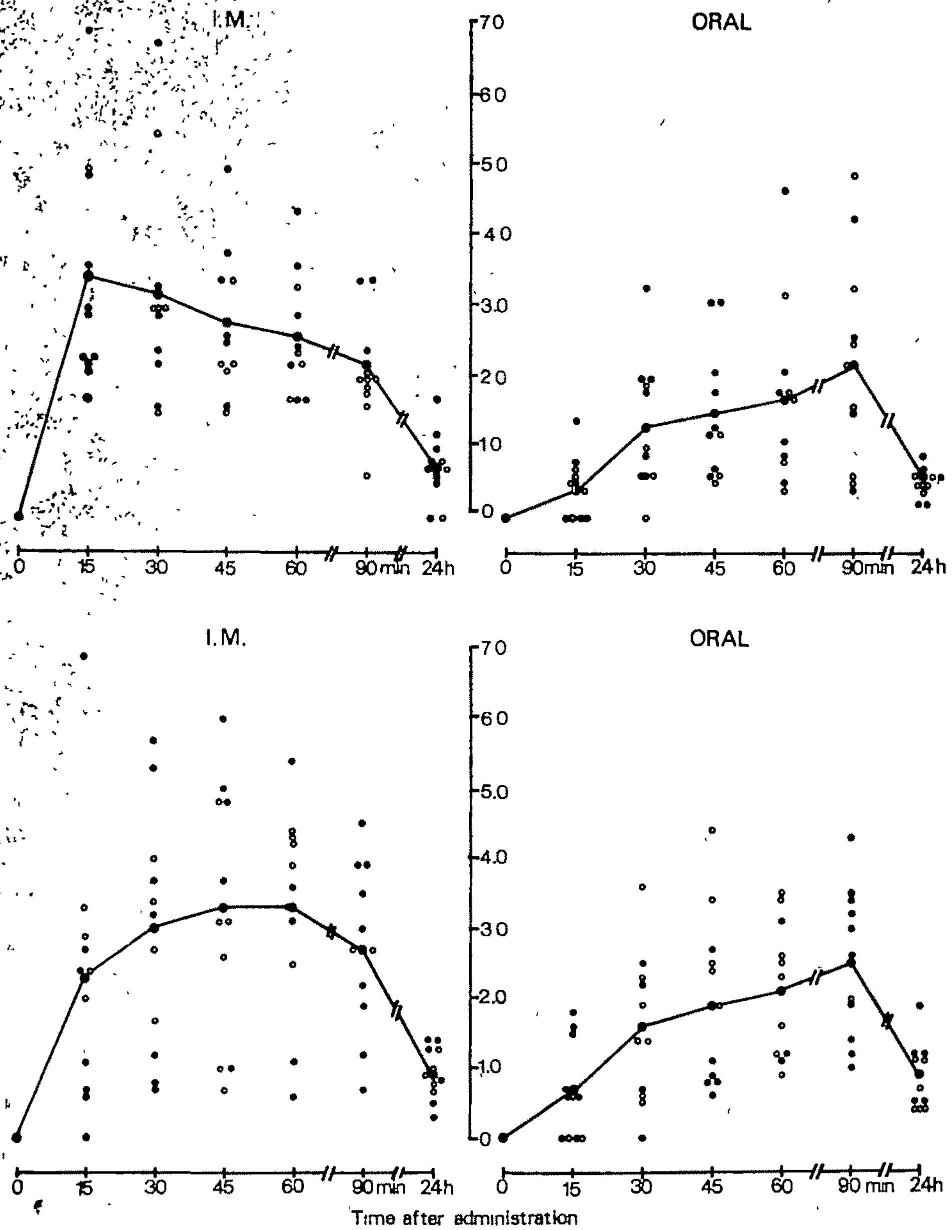


FIG. 3. Plasma concentrations of flunitrazepam (ng ml^{-1}, vertical axis) in 11 subjects (○), and mean (●——●) after flunitrazepam 0.5 (upper) or 1.0 mg (lower). Each subject received the same dose by i.m. and oral routes on different occasions.

Plasma flunitrazepam concentrations

The drug could be detected to a measurable extent up to 24 h after administration. The concentrations reached were significantly greater after i.m. than after oral administration in the first 30 min with each of the lower doses (table III; fig. 3). There was, however, no significant difference between the average concentrations after the 0.5- and 1.0-mg dose by each of the routes. The findings with flunitrazepam 2 mg involved only five subjects and were influenced strongly by one subject who had the greatest readings over the first 30–90 min with both

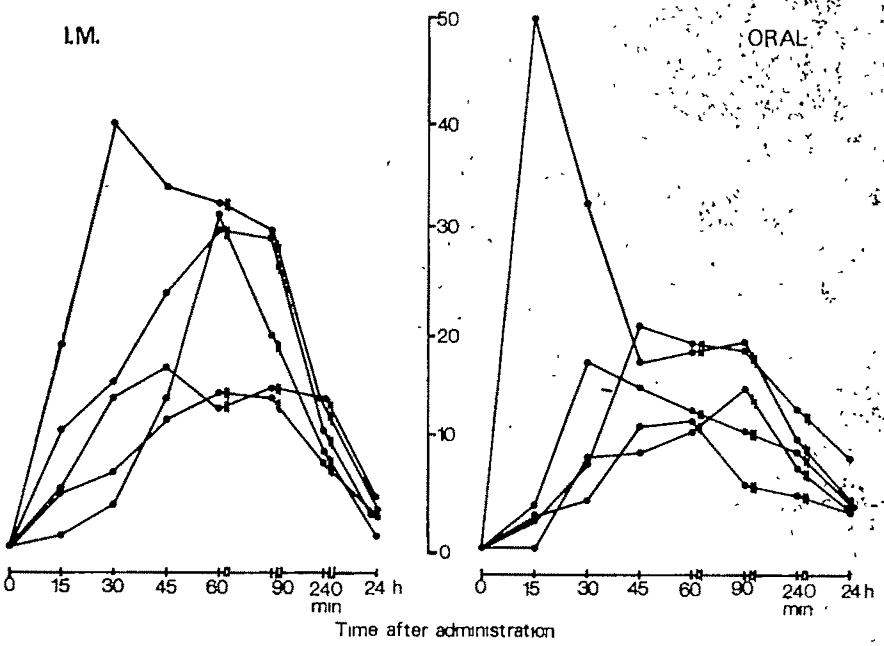


FIG. 4. Plasma concentrations of flunitrazepam (ng ml^{-1}, vertical axis) in five subjects after flunitrazepam 2-mg. Each subject received the drug by i.m. and oral routes on different occasions.

routes of administration (fig. 4). However, the average concentration was much greater with this dose. The mean readings show no significant difference between the two routes except at 90 min when the value following i.m. injection was significantly greater.

The greatest blood concentration occurred 60–90 min after administration, irrespective of route (except in the case of 0.5 mg i.m.). This was later than the time of maximum sedation, but the majority of the students were on their way home by 90 min and any sedative effect would be masked.

DISCUSSION

This study showed that flunitrazepam causes a degree of drowsiness which is strongly dose-related. In this respect it would be highly satisfactory as a premedicant. The marked dizziness which was experienced by so many of the subjects was almost exclusively associated with standing and need not influence the clinical use of the drug.

Many studies of the i.v. use of flunitrazepam have found or assumed a 10 : 1 potency ratio compared with diazepam. However, our findings would suggest that flunitrazepam 2 mg is a much more powerful sedative than diazepam 20 mg (Haslett and Dundee, 1968; Lyons, Clarke and Vulgaraki, 1975). On the other hand, volunteer subjects may be more easily sedated than patients, and it would be unjustifiable to transfer findings from one group to the other.

The comparison of the two routes of administration of flunitrazepam presents a clear difference from diazepam. The time of onset and degree of both sedation and dizziness suggest more rapid absorption by the i.m. route and this is confirmed by the blood concentrations. This is not so with diazepam, since Assaf, Dundee and Gamble (1975) showed that the peak effect of diazepam occurred more rapidly after oral than after i.m. administration. This was explained partly by the findings of Gamble, Dundee and Assaf (1975) of greater blood concentrations after oral administration. These studies showed that absorption and efficacy were greater after injection into the thigh than into the buttock, so the former route was used during the present study. The actual blood concentrations 30 min after i.m. injection of diazepam into the thigh were, however, greater than at this time after oral administration. The findings after flunitrazepam were consistent in showing a more marked effect and greater blood concentrations

10–30 min after i.m. compared with oral administration.

These studies have shown that flunitrazepam differs from diazepam, not only in producing rather more prolonged amnesia (George and Dundee, 1977), but also in its more rapid absorption from injection sites. However, it produced prolonged pain on i.m. injection—some of the volunteers who received 2 mg could still detect the bruise weeks after the study.

ACKNOWLEDGEMENTS

We are grateful to the students and staff who volunteered for these studies and to Dr Ian Pearson of Roche Products for generous supplies of flunitrazepam.

REFERENCES

Assaf, R. A. E., Dundee, J. W., and Gamble, J. A. S. (1975). The influence of the route of administration on the clinical action of diazepam. *Anaesthesia*, **30**, 152.

Clarke, R. S. J., and Lyons, S. M. (1977). Diazepam and flunitrazepam as induction agents for cardiac surgical operations. *Acta Anaesthesiol. Scand.*, **21**, 282.

Dundee, J. W., Varadarajan, C. R., Gaston, J. H., and Clarke, R. S. J. (1976). Clinical studies of induction agents. XLIII: Flunitrazepam. *Br. J. Anaesth.*, **48**, 551.

Gamble, J. A. S., Assaf, R. A. E., MacKay, J. S., Kennedy, M., and Howard, P. J. (1975). Estimation of plasma diazepam: critique of a method using gas–liquid chromatography and a benzene extraction. *Anaesthesia*, **30**, 159.

—— Dundee, J. W., and Assaf, R. A. E. (1975). Plasma diazepam levels after single dose oral and intramuscular administration. *Anaesthesia*, **30**, 164.

George, K. A., and Dundee, J. W. (1977). Relative amnesic actions of diazepam, flunitrazepam and lorazepam in man. *Br. J. Clin. Pharmacol.*, **4**, 45.

Haslett, W. H. K., and Dundee, J. W. (1968). Studies of drugs given before anaesthesia. XIV: Two benzodiazepine derivatives—chlordiazepoxide and diazepam. *Br. J. Anaesth.*, **40**, 250.

Hegarty, J. E., and Dundee, J. W. (1977). Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam and flunitrazepam. *Br. Med. J.*, **2**, 1384.

Howard, P. J., Lilburn, J. K., Dundee, J. W., Toner, W., and McIlroy, P. D. A. (1977). Estimation of plasma lorazepam by gas–liquid chromatography and a benzene extraction. *Anaesthesia*, **32**, 767.

Lyons, S. M., Clarke, R. S. J., and Vulgaraki, K. (1975). The premedication of cardiac surgical patients—a clinical comparison of four regimes. *Anaesthesia*, **30**, 459.

Stovner, J., Endresen, R., and Osterud, A. (1973). Intravenous anaesthesia with a new benzodiazepine Ro 5-4200. *Acta Anaesthesiol. Scand.*, **17**, 163.

COMPARAISON DES EFFETS SUBJECTIFS ET DES CONCENTRATIONS DE FLUNITRAZEPAM DANS LE PLASMA APRES ADMINISTRATION DE CE MEDICAMENT PAR VOIES ORALE ET INTRAMUSCULAIRE A DES VOLONTAIRES

RESUME

On a administré à des groupes de volontaires du flunitrazépam à raison de 0,5, 1 ou 2 mg soit par voie orale, soit par voie intramusculaire et on a comparé les effets qui en ont découlé. Les concentrations de ce médicament dans le plasma ont été évaluées par chromatographie en phase gazeuse–liquide sur un petit nombre de sujets. L'effet le plus frappant a été l'effet de sédation qui est allé en augmentant avec la dose, 2 mg produisant un sommeil profond, bien qu'il fut toujours possible d'éveiller les sujets. Les effets de l'administration par voie intramusculaire se sont manifestés plus tôt et durèrent quelquefois même plus longtemps que ceux qui ont suivi l'administration orale. Les vertiges ont été moins marqués que la sédation, mais ils ont augmenté en fonction de la dose. On a remarqué que la douleur était plus fréquente au moment de l'injection intramusculaire de flunitrazépam qu'avec le sérum isotonique. Les concentrations dans le plasma ont varié suivant la dose et le mode d'administration et elles ont correspondu quantitativement aux effets subjectifs. Le médicament était toujours présent en quantités mesurables 24 h après l'injection, même avec les doses les plus faibles.

VERGLEICH DER SUBJEKTIVEN EFFEKTE UND DER PLASMAKONZENTRATIONEN NACH ORALER UND INTRAMUSKULÄRER VERABREICHUNG VON FLUNITRAZEPAM AN FREIWILLIGE

ZUSAMMENFASSUNG

Die Effekte der Verabreichung von 0,5, 1,0 oder 2,0 mg Flunitrazepam entweder oral oder intramuskulär an Gruppen von Freiwilligen wurden verglichen. Die Plasmakonzentrationen der Droge wurden durch Gas-Flüssigkeitschromatographie bei einer kleineren Anzahl der Versuchspersonen geschätzt. Der auffallendste Effekt war die Sedierung, die mit der Dosis anstieg—2 mg bewirkten tiefen Schlaf, wenn die Versuchspersonen auch noch geweckt werden konnten. Die Wirkungen der intramuskulären Verabreichung waren früher erkennbar und dauerten auch manchmal länger als nach oraler Verabreichung. Schwindelgefuhl war weniger deutlich als Sedierung, stieg aber mit erhöhter Dosis an. Schmerzen bei intramuskulärer Verabreichung traten wesentlich häufiger auf als bei isotonischen Salzlösungen. Die Plasmakonzentrationen variierten je nach Dosis und Verabreichungsmethode und entsprachen qualitativ den subjektiven Effekten. Die Droge war nach 24 Stunden selbst nach der kleinsten Dosis immer noch in messbaren Mengen vorhanden.

COMPARACION DE LOS EFECTOS SUBJETIVOS Y DE LAS CONCENTRACIONES EN EL PLASMA DESPUES DE LA ADMINISTRACION ORAL E I.M. DE FLUNITRAZEPAM EN VOLUNTARIOS

SUMARIO

Se administró 0,5 1,0 ó 2,0 mg de flunitrazepam por vías oral e i.m. a unos grupos de voluntarios y se comparó sus efectos. Se estimaron las concentraciones en el plasma de la substancia por cromatografía gas–líquido, en un número menor de sujetos. El efecto más notorio fue la sedación que aumentó con la dosis, 2 mg produjeron un sueño profundo aunque fuera posible despertar a los sujetos. Los efectos de la administración i.m. aparecieron más temprano y a veces duraron por más tiempo que los registrados después de la administración oral. Los vértigos fueron menos marcados que la sedación, pero aumentaron con la dosis. La inyección i.m. de flunitrazepam causó un dolor más a menudo que con la sal metálica isotónica. Las concentraciones en el plasma variaban con la dosis y la vía de administración y correspondían cualitativamente con los efectos subjetivos. La substancia se hallaba presente aún en cantidades mensurables después de 24 h, siquiera con la dosis más pequeña.

Br. J. Anaesth. (1980), 52, 447

COMPARISON OF THE SUBJECTIVE EFFECTS AND PLASMA CONCENTRATIONS FOLLOWING ORAL AND I.M. ADMINISTRATION OF FLUNITRAZEPAM IN PATIENTS

W. A. W. McGowan, J. W. Dundee, R. S. J. Clarke and P. J. Howard

SUMMARY

The use of flunitrazepam 1 and 1.5 mg was compared as a premedicant with diazepam 10 mg and lorazepam 2.5 mg. Plasma flunitrazepam concentrations were measured after oral and i.m. administration. Flunitrazepam and diazepam had a similar onset time and duration of action, both being more rapid in onset and shorter in duration than lorazepam. I.m. flunitrazepam had a slightly greater sedative effect than oral flunitrazepam and plasma concentrations correlated well with the onset of the sedative effect by either route of administration. The i.m. injection of flunitrazepam was not as painful as that of diazepam, but slightly more painful than lorazepam. A second peak occurred at about 5 h and flunitrazepam was still detectable at 48 h. The plasma half-life was 3–4 h.

The introduction of the benzodiazepines has produced a trend to oral preanaesthetic medication. This has proved acceptable to nurses and patients and the provision of adequate sedation before anaesthesia has made these drugs acceptable to anaesthetists. Flunitrazepam has been used widely in Europe for premedication (Wickstrom, 1973; Freuchen, Ostergaard and Mikkelsen, 1976a) and for the induction of anaesthesia (Stovner, Endresen and Osterud, 1973; Freuchen, Ostergaard and Mikkelsen, 1976b). We have used it for induction (Dundee et al., 1976) but found its action to be too variable for routine use. In this study the action of flunitrazepam as a premedicant was compared with that of lorazepam and diazepam, part of the data for these last two drugs having been published previously (Dundee et al., 1977, 1979).

PATIENTS AND METHODS

Healthy patients undergoing minor gynaecological procedures not requiring sedation on the night before operation were selected for the trial on a random basis. All were of grade 1 or 2 of ASA classification (Owens, Felts and Spitznagel, 1978). Allocation to flunitrazepam 1 mg or 1.5 mg or lorazepam 2.5 mg by mouth was by random numbers and the administration of premedicant and subsequent observations were carried out with a double-blind technique. Data on the effects of flunitrazepam 2 mg and diazepam 10 mg by mouth were taken from previous studies (Dundee et al., 1977, 1979), carried out under identical conditions using the same programme of study. At the start of the trial the i.m. preparation of flunitrazepam was not available and this was included only in the later part of the study.

Following the administration of the drug the patients were visited at 20, 40, 60 and 90 min and at each visit several subjective and objective observations were made and recorded as described originally by Dundee, Moore and Nicholl (1962) and more recently by Haslett and Dundee (1968) and Morrison, Clarke and Dundee (1970). The degree of drowsiness was graded as *good*, *fair*, *slight* or *nil*. Apprehension was graded as *marked*, *moderate*, *slight* or *absent* and restlessness or excitement as *marked*, *slight* or *nil*. Based on these observations and the general behaviour of the patients, an efficacy score was allocated, ranging from 5 (good sedation, with no apprehension or excitement) to 1 (no sedation with marked apprehension or excitement, or both).

Where applicable the occurrence of persistent pain at the site of injection was graded as *marked*, *slight* or *nil*. The decrease in the systolic arterial pressure related to the premedication was graded as *nil* (0–20 mm Hg), *moderate* (21–40 mm Hg) or *severe* (41+ mm Hg). Heart rates were classified as *no tachycardia* (less than 100 beat min^{-1}), *slight tachycardia* (100–120 beat min^{-1}) and *severe tachycardia* (121+ beat min^{-1}). On these criteria a "toxic" score was assigned, ranging from 5 (patients unmanageable or having severe side-effects) to 1 (no side-effects).

W. A. W. McGowan, M.D., F.F.A.R.C.S.; J. W. Dundee, M.D., PH.D., F.F.A.R.C.S., M.R.C.P.; R. S. J. Clarke, M.D., PH.D., F.F.A.R.C.S.; P. J. Howard, F.S.A.L.T., F.I.S.T.; Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland.

0007-0912/80/040447-05 $01.00

© Macmillan Journals Ltd 1980

In addition, plasma concentrations were estimated in five patients given flunitrazepam 1 mg by mouth and in a further five of comparable age, weight and build given 1 mg i.m. Blood samples (5 ml) were withdrawn from an indwelling cannula in the antecubital fossa before the drug was administered and, following administration, at 15, 30, 45, 60, 90 and 120 min, at 1-h intervals up to 8 h and at 24 and 48 h. The blood was transferred immediately to heparinized tubes and stored at 4 °C until centrifuged—always within 4 h of sampling. The plasma was stored in non-heparinized bottles at −20 °C until the flunitrazepam concentrations were estimated. Single-stage benzene extraction and gas–liquid chromatography using lorazepam as the internal standard, as described by Clarke and colleagues (1980), was used. No other investigations were carried out in those patients in whom estimations of blood concentrations were made.

RESULTS

Table I shows that the different groups of patients were broadly comparable with respect to age and weight.

TABLE I. *Patient data.* (**From Dundee et al.*, 1979)

Benzodiazepine and dose (mg)	Route	No.	Age (yr)	Weight (kg)
Flunitrazepam 1	I.m.	50	30.5 ± 1.47	62.0 ± 1.45
Flunitrazepam 1	Oral	50	32.3 ± 1.51	61.5 ± 1.48
Flunitrazepam 1.5	Oral	20	29.6 ± 2.08	59.0 ± 2.44
Flunitrazepam 2	Oral	20	35.2 ± 2.32	57.2 ± 2.01
Diazepam* 10	Oral	50	32.9 ± 1.3	60.2 ± 1.5
Lorazepam* 2.5	Oral	100	32.8 ± 0.86	59.4 ± 0.83

Tables II and III show that flunitrazepam was more than 10 times as potent as diazepam as a hypnotic. Flunitrazepam 1 mg or 1.5 mg by mouth gave significantly ($P < 0.05$) better sedation than diazepam 10 mg at most times (except flunitrazepam 1 mg at 20 min). Similarly, flunitrazepam was significantly better than lorazepam ($P < 0.0005$) at all times except flunitrazepam 1 mg at 90 min ($\chi^2 = 6.1534$; $P < 0.025$).

Flunitrazepam i.m. had a slightly greater sedative effect than the same dose given by mouth (table II, fig. 1). Generally speaking, flunitrazepam 1.5 mg produced a slightly better effect than 1.0 mg, but the difference was only significant at the 40-min observation ($\chi^2 = 4.4884$; $P < 0.05$).

The plasma concentrations (fig. 2) of flunitrazepam correlated well with the onset of the sedative effect by either route of administration. A second peak occurred at about 5 h and flunitrazepam was detected in the blood up to 48 h. The plasma half-life was 3–4 h calculated over the 1–5 h period before the second peak.

TABLE II. *Frequency (%) of notable (good and fair) drowsiness following various doses of flunitrazepam, diazepam and lorazepam.* (**From Dundee et al.*, 1979)

Benzodiazepine and dose (mg)	Route	20 min	40 min	60 min	90 min
Flunitrazepam 1	I.m.	26	62	74	88
Flunitrazepam 1	Oral	18	72	86	86
Flunitrazepam 1.5	Oral	35	95	100	100
Flunitrazepam 2	Oral	40	70	80	90
Diazepam 10	Oral	8	40	64	60
Lorazepam 2.5*	Oral	2	25	44	67

TABLE III. *Mean efficacy scores at varying intervals following oral administration of three benzodiazepines*

Benzodiazepine and dose (mg)	20 min	40 min	60 min	90 min
Flunitrazepam 1	2.7	4.2	4.6	4.3
Diazepam 10	2.3	3.2	3.8	3.8
Lorazepam 2.5	2.3	2.9	3.7	3.8

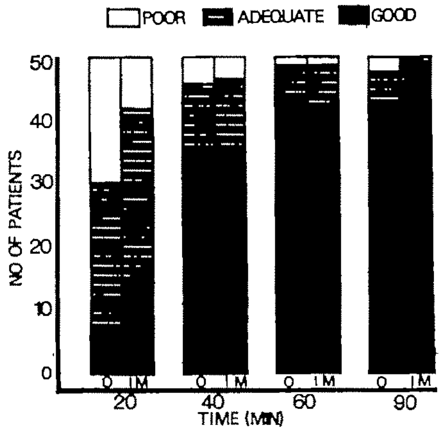


FIG. 1. Overall sedative effect of flunitrazepam 1 mg given either by mouth or by i.m. injection.

The area under the plasma concentration/time curve following the oral route was 26.0 ± 5.51 $\mathrm{ng\,h^{-1}}$ for the period 0–8 h and 49.9 $\mathrm{ng\,h^{-1}}$ for 0–24 h. The respective values following the i.m. route were 31.4 ± 6.34 $\mathrm{ng\,h^{-1}}$ and 65.0 ± 14.49 $\mathrm{ng\,h^{-1}}$. These differences were not significant.

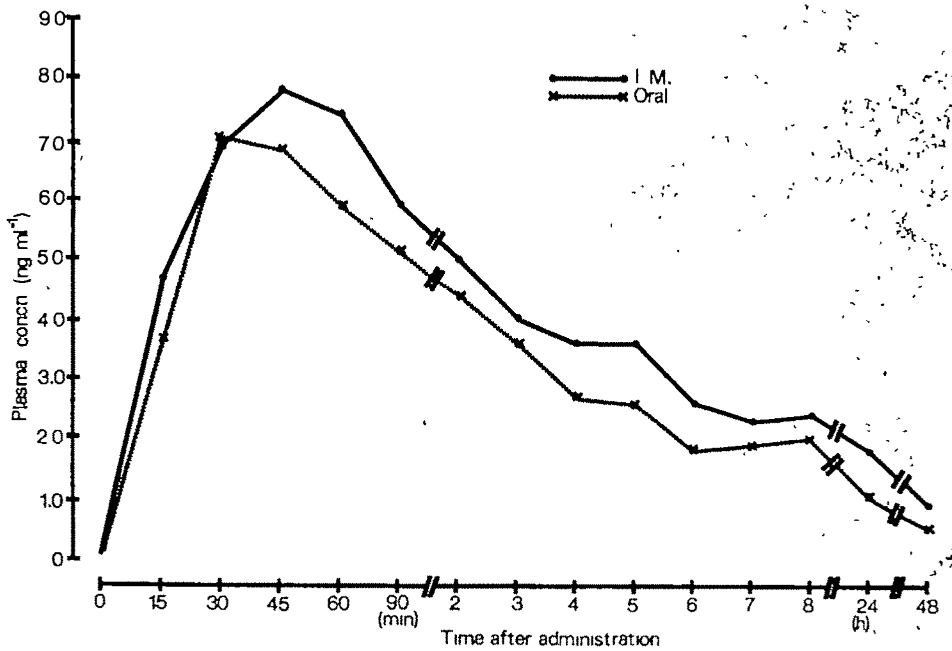


FIG. 2. Plasma concentrations of flunitrazepam following 1 mg given either by mouth or by i.m. injection.

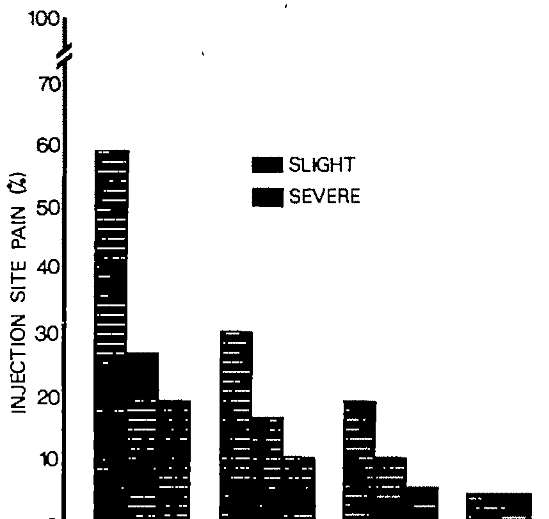


FIG. 3. Frequency of pain at the injection site at various times following injection of benzodiazepines.

Figure 3 shows the percentage frequency of pain at the injection site after flunitrazepam 1 mg, diazepam 10 mg or lorazepam 4 mg. The injection of flunitrazepam was not as painful as that of diazepam, but slightly more so than lorazepam and with a similar duration to diazepam. No other side-effects were observed.

DISCUSSION

In a previous study Dundee and colleagues (1976) found that flunitrazepam was unsatisfactory as an induction agent because of the slow onset of action of 90–120 s and great individual variation among patients. The present study shows the efficacy of flunitrazepam as a premedicant as compared with diazepam and lorazepam.

Flunitrazepam administered by mouth had an onset and duration of action similar to diazepam, but 1 mg was a better sedative than diazepam 10 mg. There would appear to be little advantage in using doses of flunitrazepam greater than 1.5 mg. Like diazepam, flunitrazepam had a more rapid onset of action than lorazepam and a shorter duration of action.

Diazepam has been shown to be absorbed more rapidly after the oral route than after the i.m. (Kanto, 1974) and this is in keeping with the clinical findings of McCaughey and Dundee (1972) and Assaf, Dundee and Gamble (1975). Flunitrazepam has a slightly more rapid clinical effect after i.m. injection than when given by mouth and this finding is substantiated by the slightly greater plasma concentrations after i.m. injection.

The plasma concentrations of flunitrazepam have a profile very similar to those of diazepam with a second peak at about 5 h, probably as a result of entero-hepatic recirculation, and detectable amounts in the plasma up to 48 h. This would indicate that flunitrazepam given in regular doses would accumulate in the blood as does diazepam. The plasma half-life is shorter than that of diazepam, but it must be remembered that we studied relatively young patients and that the plasma half-life of benzodiazepines increases with age.

Our findings would suggest that flunitrazepam 1 mg or 1.5 mg by mouth is an acceptable premedicant and that the small advantage to be gained from i.m. injection is offset by over 25% frequency of pain at the site of injection.

ACKNOWLEDGEMENTS

We are grateful to the doctors and nurses of the Musgrave Park and Belfast City Hospitals for co-operation during the studies and to Dr Ian Pearson, Roche Products, for the generous supply of flunitrazepam.

REFERENCES

Assaf, R. A. E., Dundee, J. W., and Gamble, J. A. S. (1975). The influence of the route of administration on the clinical action of diazepam. *Anaesthesia*, **30**, 152.

Clarke, R. S. J., Dundee, J. W., McGowan, W. A. W., and Howard, P. J. (1980). Comparison of the subjective effect and plasma concentrations following oral and i.m. administration of flunitrazepam in volunteers. *Br. J. Anaesth.*, **52**, 437.

Dundee, J. W., George, K. A., Varadarajan, C. R., Clarke, R. S. J., and Nair, S. G. (1976). Anaesthesia and amnesia with flunitrazepam. *Br. J. Anaesth.*, **48**, 266.

—— Johnston, H. M. L., Lilburn, J. K., Nair, S. G., and Scott, M. G. (1977). A placebo-controlled comparison of the sedative properties of three benzodiazepines—lorazepam, flunitrazepam and fosazepam. *Br. J. Clin. Pharmacol.*, **4**, 706.

—— McGowan, W. A. W., Lilburn, J. K., McKay, A. C., and Hegarty, J. E. (1979). Comparison of the action of diazepam and lorazepam. *Br. J. Anaesth.*, **51**, 439.

—— Moore, J., and Nicholl, R. M. (1962). Studies of drugs given before anaesthesia. I: A method of preoperative assessment. *Br. J. Anaesth.*, **34**, 458.

Freuchen, I., Ostergaard, J., and Mikkelsen, B. O. (1976a). Flunitrazepam as evening premedication. Report of a controlled clinical comparison with nitrazepam and allypropymal. *Ugeskr. Laeg.*, **138**, 2232.

—— —— —— (1976b). Flunitrazepam (Rohypnol) compared with enibomal (Narcodorm) as an anaesthetic induction agent: a controlled clinical trial. *Curr. Ther. Res.*, **20**, 36.

Haslett, W. H. K., and Dundee, J. W. (1968). Studies of drugs given before anaesthesia. XIV: Two benzodiazepine derivatives—chlordiazepoxide and diazepam. *Br. J. Anaesth.*, **40**, 250.

Kanto, J. (1974). Plasma levels of diazepam after oral and intramuscular administration. *Br. J. Anaesth.*, **46**, 817.

McCaughey, W., and Dundee, J. W. (1972). Comparison of the sedative effects of diazepam given by the oral and intramuscular routes. *Br. J. Anaesth.*, **44**, 901.

Morrison, J. D., Clarke, R. S. J., and Dundee, J. W. (1970). Studies of drugs given before anaesthesia. XXI: Droperidol. *Br. J. Anaesth.*, **42**, 730.

Owens, W. D., Felts, J. A., and Spitznagel, E. L. (1978). ASA physical status classifications. *Anesthesiology*, **49**, 239.

Stovner, J., Endresen, R., and Osterud, A. (1973). Intravenous anaesthesia with a new benzodiazepine R05-4200. *Acta Anaesthesiol. Scand.*, **17**, 163.

Wickstrom, E. (1973). Flunitrazepam (R05-4200)—et nytt hypnotikum. *Tidsskr. Norske Laegefor.*, **93**, 1494.

COMPARAISON DES EFFETS SUBJECTIFS ET DES CONCENTRATIONS DE FLUNITRAZEPAM DANS LE PLASMA APRES ADMINISTRATION DE CE MEDICAMENT PAR VOIES ORALE ET INTRAMUSCULAIRE A DES MALADES

RESUME

L'usage du flunitrazépam en tant que prémédication administrée à des doses de 1 et de 1,5 mg a été comparé au diazépam—doses de 10 mg—et au lorazépam—doses de 2,5 mg. Les concentrations de flunitrazépam dans le plasma ont été mesurées après administration de ce médicament par voie orale et par voie intramusculaire. Le flunitrazépam et le diazépam ont eu un temps d'induction et une durée d'action similaires, tous les deux étant plus rapides du point de vue induction et plus courts du point de vue durée que le lorazépam. Le flunitrazépam administré par voie intramusculaire a eu un effet sédatif légèrement plus grand que ce même médicament administré par voie orale et ses concentrations dans le plasma ont été en bonne corrélation avec le commencement de l'effet sédatif, quelle que soit la voie utilisée pour l'administration. L'injection intramusculaire de flunitrazépam n'a pas été aussi douloureuse que celle de diazépam, mais tout de même plus douloureuse que le lorazépam. Une seconde pointe s'est produite environ 5 h plus tard, et on pouvait encore déceler le flunitrazépam 48 h après son administration. La demi-vie dans le plasma a été de 3 à 4 h.

VERGLEICH DER SUBJEKTIVEN EFFEKTE UND DER PLASMAKONZENTRATIONEN NACH ORALER UND INTRAMUSKULÄRER VERABREICHUNG VON FLUNITRAZEPAM AN PATIENTEN

ZUSAMMENFASSUNG

Die Verwendung von 1 mg und 1,5 mg Flunitrazepam wurde als Vorbehandlungsmittel mit 10 mg Diazepam und 2,5 mg Lorazepam verglichen. Die Plasmakonzentrationen von Flunitrazepam wurden nach oraler und nach intramuskulärer Verabreichung gemessen. Flunitrazepam und Diazepam hatten eine ähnliche Anlauf- und Wirkungsdauer, und bei beiden Drogen war die Anlaufzeit schneller und die Wirkungsdauer kürzer als bei Lorazepam. Intramuskulär gegebens Flunitrazepam hatte eine etwas höhere Sedativ-

wirkung als oral gegebenes, und die Plasmakonzentrationen waren gut abgestimmt auf das Einsetzen der Sedativwirkung nach beiden Verabreichungsmethoden. Die intramuskuläre Injektion von Flunitrazepam war weniger schmerzhaft als die von Diazepam, aber etwas schmerzhafter als die von Lorazepam. Ein zweiter Gipfel ergab sich nach etwa 5 Stunden, und das Flunitrazepam war nach 48 Stunden immer noch feststellbar. Die Plasma-Halbwertzeit betrug 3–4 Stunden.

COMPARACION DE LOS EFECTOS SUBJETIVOS Y DE LAS CONCENTRACIONES EN EL PLASMA DESPUES DE LA ADMINISTRACION ORAL E I.M. DE FLUNITRAZEPAM EN PACIENTES

SUMARIO

Se hizo una comparación del uso de 1 y 1,5 mg de flunitrazepam como premedicación con 10 mg de diazepam y 2,5 mg de lorazepam. Las concentraciones de flunitrazepam en el plasma fueron medidas después de su administración oral e i.m. El flunitrazepam y el diazepam produjeron la anestesia en el mismo plazo y tuviera una duración de acción similar, ambos dando lugar a la anestesia más rápidamente que el lorazepam pero sí de duración más corta. El flunitrazepam i.m. tuvo un efecto sedativo un poco mayor que el flunitrazepam oral y las concentraciones en el plasma fueron correlativas con el comienzo del efecto sedativo por cualquiera de las dos vías de administración. La inyección i.m. de flunitrazepam no era tan dolorosa como la de diazepam, pero sí un poco más dolorosa que la de lorazepam. Un segundo tope se registró cerca de 5 h después y se podía todavía detectar el flunitrazepam después de 48 h. La media-vida del plasma era de 3–4 h.

Br. J. Anaesth. (1980), **52**, 453

A DOUBLE-BLIND COMPARISON BETWEEN FENTANYL AND BUPRENORPHINE IN ANALGESIC-SUPPLEMENTED ANAESTHESIA

B. KAY

SUMMARY

Buprenorphine 0.3 mg or fentanyl 0.125 mg i.v. were used to supplement nitrous oxide anaesthesia in a double-blind investigation of 40 patients undergoing major abdominal surgery. Initially both narcotics appeared to suppress tachycardia and increased arterial pressure in response to surgery, but 80% of the patients who received fentanyl eventually required a further supplement of halothane 0.5%, whereas no patient who received buprenorphine required halothane. Recovery from anaesthesia was similar in both groups, but the duration of analgesia after operation was significantly greater after buprenorphine than after fentanyl.

Buprenorphine is a narcotic analgesic with high potency and a limited agonist effect (Cowan, Lewis and MacFarlane, 1977); it is not hallucinogenic (Jasinski, Pevnick and Griffiths, 1978). It has been shown to be effective in treating or delaying the onset of pain after operation, and to possess a long duration of action (Kay, 1978). The author's personal experience is that buprenorphine is an effective supplement to nitrous oxide for the maintenance of anaesthesia. The present study was a double-blind comparison between buprenorphine and fentanyl used in this way.

Buprenorphine 0.3 mg has been shown to produce approximately the same effects as morphine 12.5 mg (Orwin, Orwin and Price, 1976), and fentanyl is about 100 times as potent as morphine. Buprenorphine 0.3 mg was therefore compared with fentanyl 0.125 mg.

PATIENTS AND METHODS

Forty patients undergoing abdominal surgery were investigated. They were aged 18–70 yr and none suffered from pulmonary, cardiac, renal or hepatic disease which would contraindicate the anaesthetic technique employed. No patient was known to be tolerant or habituated to narcotics. They were divided randomly into groups A and B.

Anaesthetic technique

No premedication was used. Anaesthesia was induced with methohexitone 1 mg kg^{-1}, alcuronium 15 mg and either buprenorphine 0.3 mg (group A) or fentanyl 0.125 mg (group B). The analgesic drug was presented to the anaesthetist as a 2.5-ml solution in a syringe, and he was thus unaware of the identity of the drug. The trachea was intubated and the lungs were ventilated to maintain normocarbia using nitrous oxide 75% in oxygen. Supplements of alcuronium were given if indicated and halothane 0.5% was added on clinical indications of inadequate analgesia such as increasing heart rate or arterial pressure, sweating, lacrimation, movement and increased pupil size. Towards the end of operation ventilation was reduced to increase Pa_{CO_2}, atropine 1.2 mg and neostigmine 2.5 mg were given i.v. as the skin incision was sutured and nitrous oxide was discontinued at the end of surgery.

Observations

Heart rate was monitored continuously and recorded every 5 min, with systolic arterial pressure. If halothane was used, the indications were recorded, as was the time at which it was first required. After operation, the time to resumption of spontaneous ventilation was measured, from the onset of tachycardia after the administration of atropine. The time to spontaneous waking, usually indicated by an obvious awareness of the endotracheal tube, and measured from the time of discontinuation of anaesthetic gases was recorded. Note was made of the time of administration of a narcotic analgesic for the relief of postoperative pain.

RESULTS

Groups A and B were statistically comparable (table I). There was a similar distribution of type of operation between the groups, the commonest being biliary or uterine procedures.

B. KAY, M.B., CH.B., F.F.A.R.C.S., Department of Anaesthetics, Research and Teaching Block, Withington Hospital, West Didsbury, Manchester M20 8LR.

0007–0912/80/040453–05 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Age, sex, and weight distribution, and duration of anaesthesia in the 40 patients. Mean values* ± SEM

Group	Age (yr)	Sex	Weight (kg)	Duration of anaesthesia (min)
Buprenorphine	47.75 ± 4	14 F, 6 M	64.6 ± 1.7	86.65 ± 13.8
Fentanyl	43.75 ± 4.1	14 F, 6 M	64.4 ± 1.3	88.5 ± 11.1

Cardiovascular responses. In the analysis of results, changes occurring in the first 10 min of anaesthesia and after the use of halothane were ignored. The most significant differences in the cardiovascular responses to surgery between the groups were seen when mean maximum and minimum values recorded were compared (fig. 1).

Before operation, arterial pressure was similar in both groups. Patients in both groups exhibited similar minimum values, significantly lower than the initial values. Mean maximum values differed significantly between the groups, however, the buprenorphine group having smaller and the fentanyl group greater values than initially, reflecting an increased frequency of a hypertensive response to surgical stimulation.

Changes in heart rate showed a slightly different pattern. Only in the buprenorphine group were minimum values significantly smaller than the pre-induction values, suggesting that buprenorphine 0.3 mg was more likely to produce bradycardia than was fentanyl 0.125 mg. Mean maximum values in the fentanyl group were significantly greater than the initial values in either group, and also those recorded in the buprenorphine group, again indicating that buprenorphine 0.3 mg was more effective than fentanyl 0.125 in suppressing the cardiovascular responses to surgery.

This was confirmed when the halothane requirements of the two groups were compared (table II). Eighty per cent of patients who received fentanyl were given halothane, after a mean duration of about

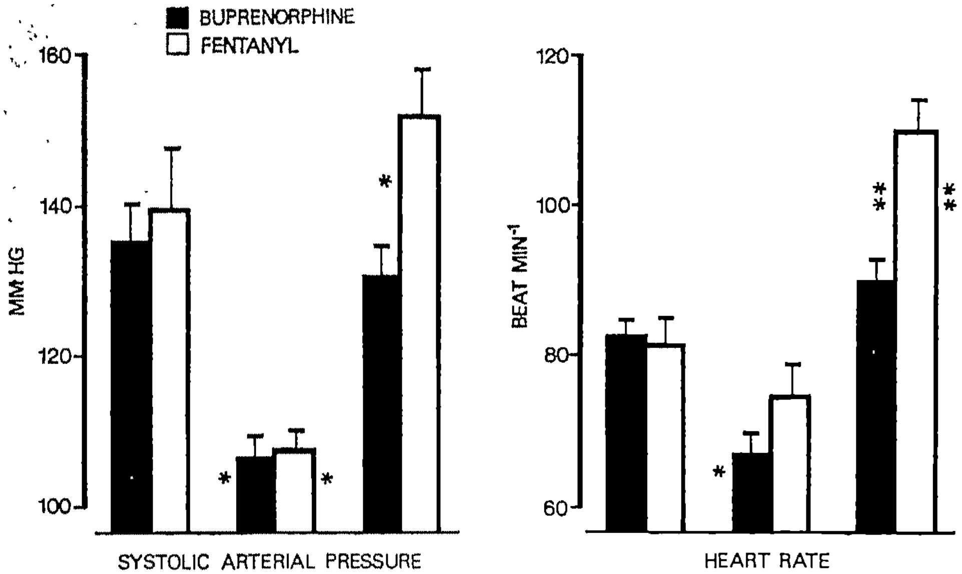


FIG. 1. Maximum changes in recorded systolic arterial pressure and heart rate (beat min^{-1}) (mean values + SEM). Pre-induction values (first columns) are followed by minimum values recorded (second columns) and maximum values (third columns). * $P < 0.01$; ** $P < 0.001$. Asterisks alongside the columns indicate significant changes from pre-induction values; asterisks between the columns indicate significant differences between the groups.

40 min, whilst no patient who received buprenorphine required a further supplement.

TABLE II. *Frequency and mean time for requirement of halothane* 0.5%

Group	Frequency of use	Time of use
Buprenorphine	0	—
Fentanyl	16 (80%)	40.6 ± SEM 3.7 min

Recovery times were similar in both groups (table III), although the use of halothane in so many of the fentanyl group undoubtedly increased the waking time in those patients.

TABLE III. *Recovery from anaesthesia. Mean times (± SEM) to onset of spontaneous breathing and waking*

Group	Breathing (min)	Waking (min)
Buprenorphine	1.86 ± 0.26	3.23 ± 0.69
Fentanyl	1.58 ± 0.15	3.92 ± 1.08

A further highly significant difference between the groups occurred in time of administration of the first narcotic analgesic after operation (table IV). Nineteen of the fentanyl group required a narcotic in the first 24 h after operation, and the mean interval between induction of anaesthesia and the first injection was 2.8 h. Fifteen of the buprenorphine group received a narcotic in the 24-h period after operation, and the mean interval was 12.1 h.

TABLE IV. *Mean times (± SEM) from induction of anaesthesia to the administration of the first narcotic analgesic after anaesthesia*

Group	No. of patients	Time of narcotic (h)
Buprenorphine	15	12.1 ± 1.5
Fentanyl	19	2.8 ± 0.48

Complications

In two patients, one of each group, recovery of consciousness was unduly prolonged (12 and 15 min), and was associated with hypothermia (34 °C). In a further three patients (two fentanyl, one buprenorphine) a heart rate of 40 beat min^{-1} or less occurred. The patient who received buprenophine was treated with atropine 0.6 mg i.v. In the others bradycardia was transient, but in each case was associated with supraventricular extrasystoles.

DISCUSSION

In this series, buprenorphine 0.3 mg proved to be an adequate analgesic supplement to nitrous oxide in oxygen anaesthesia. Not only were excessive cardiovascular and other clinical responses to surgical stimulation sufficiently suppressed, but the technique provided satisfactory analgesia in the period after operation, allowing most patients a tranquil and relatively pain-free period throughout the day of operation. Also, recovery of both consciousness and spontaneous ventilation was rapid.

It was not expected that supplementation with fentanyl 0.125 mg would produce similar results. Such a dose has very transient effects, and would not be expected to provide adequate reflex suppression in operations of this nature and duration (Kay and Rolly, 1977). Many anaesthetists would suggest that as much as five times this dose would be more appropriate. The 40-min duration of effect, frequent need for further supplementation and early use of analgesia after operation could be expected in this group.

It is surprising that such small doses of either narcotic were adequate to maintain reasonable suppression of tachycardia and increased arterial pressure in response to surgery. Suppression was not absolute; transient sweating was commonly observed in these patients, who had not received atropine, but this was not regarded as an indication for further supplementation unless accompanied by increases in arterial pressure, heart rate and lacrimation. Increases in heart rate occurred mainly in the group who received fentanyl, but bradycardia, presumably in response to stimulation, occurred in both groups and was occasionally accompanied by extrasystoles. This response can of course be suppressed by atropine and should perhaps be regarded as an indication for further analgesia.

The need for further analgesic supplements after buprenorphine presents difficulty. Knowing that such indications may persist for a few minutes only, it may be inappropriate to use a further dose of buprenorphine, which may not be effective for 10–15 min after i.v. injection (Cowan, Lewis and MacFarlane, 1977). I.v. fentanyl should be effective, and small doses of fentanyl should increase the analgesic effect of small doses of buprenorphine, although buprenorphine will act as an antagonist after large doses of fentanyl (De Castro and Parmentier, 1976).

A further problem in the use of buprenorphine as an analgesic supplement to anaesthesia is the selection of the most appropriate dose. Buprenorphine is a narcotic with limited agonist effect, but the dose at which this limitation occurs in man is not known. Further investigation is required to determine if 0.6 mg would be more effective in suppressing autonomic reflexes during surgery. It would seem unlikely that suppression of hormonal responses to surgery, such as can be obtained by large doses of fentanyl (Hall et al., 1978), can be produced by buprenorphine. On the other hand, the limited respiratory depression associated with buprenorphine alone will normally confer a degree of safety in the period after operation which is not seen after large doses of other narcotics. Interactions with other drugs do occur, however, and serious respiratory depression has been observed after the combination of buprenorphine with halothane, and with diazepam. Buprenorphine has been shown to produce more drowsiness than does morphine (Kay, 1978) and this constitutes an advantage in reducing the risk of awareness during nitrous oxide and oxygen maintenance of anaesthesia. No patient in this series complained of having been aware during operation.

The long period of analgesia after operation in the buprenorphine-treated patients accords with previous experience and is a considerable advantage of this technique. By using buprenorphine as the analgesic supplement during anaesthesia, prolonged analgesia after operation can be obtained without the possibility of summation with, or antagonism of, other narcotics used as analgesic supplements.

This investigation indicates that buprenorphine 0.3 mg has several advantages when used to supplement nitrous oxide, oxygen and relaxant anaesthesia, but further experience and investigation appear to be necessary to determine the best dose and methods of application.

ACKNOWLEDGEMENT

I thank Reckitt and Colman Ltd, Hull, England, for the supplies of buprenorphine used in this investigation.

REFERENCES

Cowan, A., Lewis, J. W., and MacFarlane, I. R. (1977). Agonist and antagonist properties of buprenorphine, in new antinociceptive agents. *Br. J. Pharmacol.*, **60**, 537.

De Castro, J., and Parmentier, P. (1976). Buprenorphine; in *Analgesic Anaesthesia*; *Anesthésie et Réanimation Practique*, vol. 7 (ed. J. De Castro) p. 103. Belgium: Soc. d'Anesthésie de Charleroi.

Hall, G. M., Young, C., Holdcroft, A., and Alaghband-Zadeh, J. (1978). Substrate mobilisation during surgery. A comparison between halothane and fentanyl anaesthesia. *Anaesthesia*, **33**, 924.

Jasinski, D. R., Pevnick, J. S., and Griffiths, J. D. (1978). Human pharmacology and abuse potential of the analgesic buprenorphine. A potential agonist for treating narcotic addiction. *Arch. Gen. Psychiatr.*, **35**, 501.

Kay, B. (1978). A double-blind comparison of morphine and buprenorphine in the prevention of pain after operation. *Br. J. Anaesth.*, **50**, 605.

—— Rolly, G. (1977). Duration of action of analgesic supplements to anaesthesia. *Acta Anaesthesiol. Belg.*, **28**, 25.

Orwin, J. M., Orwin, J. and Price, M. (1976). A double-blind comparison of buprenorphine and morphine in conscious subjects following intramuscular administration. *Acta Anaesthesiol. Belg.*, **27**, 171.

COMPARAISON A DOUBLE INCONNUE ENTRE LE FENTANYL ET LA BUPRENORPHINE POUR LES ANESTHESIES COMPLETEES PAR DES AGENTS ANALGESIQUES

RESUME

On a utilisé de la buprénorphine à raison de 0,3 mg, ou du fentanyl à raison de 0,125 mg, administré par voie intraveineuse pour compléter l'anesthésie au protoxyde d'azote au cours d'une étude à double inconnue effectuée sur 40 patients devant subir des interventions chirurgicales majeures à l'abdomen. A l'origine, les deux narcotiques ont semblé supprimer la tachycardie et augmenter la pression artérielle en réaction à l'intervention, mais 80% des patients auxquels on avait administré du fentanyl ont éventuellement eu besoin d'un autre supplément d'halothane à 0,5%, alors qu'aucun des patients ayant reçu de la buprénorphine n'a eu besoin d'halothane. La reprise de conscience qui a suivi l'anesthésie a été similaire dans les deux groupes, mais la durée de l'analgésie après l'opération a été beaucoup plus longue après l'administration de buprénorphine qu'après l'administration de fentanyl.

EIN DOPPELBLIND-VERGLEICH ZWISCHEN FENTANYL UND BUPRENORPHIN BEI EINER DURCH ANALGETISCHE MITTEL ERGÄNZTEN ANÄSTHESIE

ZUSAMMENFASSUNG

Buprenorphin 0,3 mg oder Fentanyl 0,125 mg wurden intravenös verabreicht, um eine Stickoxyd-Narkose in einem Doppelblind-Versuch zu ergänzen, bei 40 Patienten, die sich grosseren Unterleibsoperationen unterzogen. Anfänglich schienen beide Drogen Tachykardie zu unterdrücken und den arteriellen Druck als Reaktion auf den Eingriff zu erhöhen, doch benotigten 80% der Patienten, die Fentanyl erhalten hatten, einen weiteren Zusatz von 0,5% Halothan, was bei keinem der Patienten nötig war, die Buprenorphin erhalten hatten. Erholung aus der Narkose war bei beiden Gruppen ahnlich, aber die schmerzlindernde Wirkung nach der Operation war auf Buprenorphin wesentlich länger andauernd als auf Fentanyl.

UNA COMPARACION DOBLE-CIEGA ENTRE EL FENTANILO Y LA BUPRENORFINA EN LA ANESTESIA COMPLEMENTADA POR ANALGESICOS

SUMARIO

Se usó 0,3 mg de buprenorfina ó 0,125 mg de fentanilo por vía i.v. para complementar la anestesia por óxido nitroso en una investigación doble-ciega de 40 pacientes sometidos a cirujía abdominal mayor. Al principio, ambos narcóticos parecieron suprimir la taquicardia y aumentar la presión arterial en respuesta a la cirujía, pero el 80% de los pacientes que habían recibido fentanilo necesitaron eventualmente un complemento adicional de halotano al 0,5%, mientras que ningún paciente que había recibido buprenorfina necesitó de halotano. La recuperación después de la anestesia fue similar en ambos grupos, pero la duración de la analgesia después de la operación fue mucho mayor con la buprenorfina que con el fentanilo.

Br. J. Anaesth. (1980), **52**, 459

AN UNUSUAL CASE OF MENDELSON'S SYNDROME

R. S. VAUGHAN, G. A. D. REES AND G. L. WILLIAMS

SUMMARY

A patient aspirated soup 36 h after delivery, developed Mendelson's syndrome but survived. She was small and fat and was immobilized in bed for longer than usual because of inadvertent dural puncture; these factors are thought to have predisposed to the accident.

Pulmonary aspiration occurring in a conscious healthy patient late in the period following Caesarean section is extremely rare. An inadvertent dural tap, which occurred during the establishment of extradural analgesia in labour, contributed to this serious complication.

CASE REPORT

A 29-year-old healthy primigravida of short stature (height 155 cm, weight 77 kg) was admitted in early labour at 39 weeks' gestation. Labour became established slowly and when the cervix was 5 cm dilated the patient requested extradural analgesia.

The first attempt at establishing continuous lumbar extradural analgesia resulted in a dural tap, but a second attempt was successful. After 2 h the cervix became fully dilated. One-and-a-half hours later the head was still palpable abdominally and an attempt at forceps delivery failed.

Caesarean section was performed under general anaesthesia with no untoward event. A live male infant, birth weight 2.9 kg was delivered with Apgar scores of 7 at 1 min and 10 at 5 min.

The dural tap was treated with an extradural infusion of Hartmann's solution 1.5 litre for a period of 34 h post-partum. The patient was nursed on her right side and received oral fluids only. The extradural cannula was then removed and she was further advised to remain in bed until the following day.

The patient had received papaveretum 20 mg i.m. for relief of pain after operation at 07.00 h and nothing thereafter until she received dihydrocodeine (DF118) 60 mg orally at 18.00 h.

While drinking soup (37 h after delivery and 45 min after receiving DF118 orally), the patient suddenly choked. Fifteen minutes later she complained of central chest pain and dyspnoea. On examination, the only positive findings were tachycardia, tachypnoea and course crepitations on the right side of the chest. The chest x-ray and e.c.g. were normal. Aspiration pneumonitis or pulmonary embolism were considered, although no definite diagnosis was made. The patient was treated prophylactically with antibiotics and oxygen therapy.

Over the following 12 h her condition deteriorated and a diagnosis of aspiration pneumonitis was made. The patient was admitted to the Intensive Care Unit with respiratory failure.

Ventilation was controlled artificially and cardiopulmonary monitoring commenced. A nasogastric tube was passed and the gastric contents were found to have a pH of 1.5. Therapy included steroids, sedatives and muscle relaxants.

The management of artificial ventilation proved difficult. In the first week, an increased inspired oxygen concentration and positive end expiratory pressure (PEEP) were required to keep the arterial oxygen tension greater than 9.3 kPa (70 mm Hg). There was no difficulty in maintaining a normal arterial $P\text{CO}_2$.

Parenteral nutrition was introduced early in the management and included the infusion of albumin, potassium and blood.

Tracheotomy was performed after 7 days of orotracheal intubation. The respiratory condition subsequently improved and artificial ventilation was gradually discontinued using intermittent mandatory ventilation. The tracheostomy was sealed 9 days later. The patient was transferred to the obstetric ward from whence she was discharged after 24 days.

DISCUSSION

The maintenance of a satisfactory arterial oxygen tension in such patients may be difficult as aspiration pneumonitis is associated with a loss of intravascular

---

R. S. VAUGHAN, M.B., B.S., F.F.A.R.C.S.; G. A. D. REES, M.B., B.CH., F.F.A.R.C.S.; Department of Anaesthetics. G. L. WILLIAMS, M.D., F.R.C.O.G.; Department of Obstetrics and Gynaecology. University Hospital of Wales, Heath Park, Cardiff CF4 4XW.

0007-0912/80/040459-02 $01.00

© Macmillan Journals Ltd 1980

albumin and interstitial pulmonary oedema (Geer et al., 1976). This is the rationale for the therapeutic triad of PEEP, diuretics and i.v. albumin.

Lung function tests performed at 2 months and at 1 and 2 years after delivery (table I) showed a gradual improvement, although the residual volume and transfer factor (ml min^{-1} mm Hg^{-1}) remained small. Although there is no information concerning previous lung function tests, these results suggest that a considerable amount of permanent lung damage has occurred.

TABLE I. *Lung function data. OBS = observed; PRED = predicted; % = observed/predicted (%)*

	Residual volume (litre)			Transfer factor for CO (ml min^{-1} mm Hg^{-1})		
	OBS	PRED	%	OBS	PRED	%
Nov. 25, 1976	0.65	1.10	59	13.5	25.7	53
Sept. 28, 1977	0.91	1.36	67	15.84	25.62	62
Aug. 1978	0.73	1.34	54	14.1	25.3	56

Aspiration pneumonitis, although not uncommon in seriously ill patients, is rare in healthy conscious surgical patients (Clark, 1963). Aspiration of gastric contents and oropharyngeal secretions into the lungs is a common occurrence, usually unrecognized and without any ill-effects. The decisive factors which determine the extent of pulmonary complications are the frequency, volume and composition of the aspirate (Bartlett and Gorbach, 1975).

In this patient it was not possible to determine whether aspiration was a result of inhalation during feeding or a combination of regurgitation and inhalation of gastric contents. However, there were factors present which might have predisposed to regurgitation. These included delayed gastric emptying (Keats, Telford and Kurosu, 1957), increased gastric acidity (Blouw et al., 1976; Rennie et al., 1979) and increased intra-abdominal pressure (Beischer and Mackay, 1978). Furthermore, any tendency to oesophageal reflux will be augmented by short stature, the use of analgesics (Hall et al., 1975) and, possibly, the nursing position.

Finally, we would suggest that attention should be given to increasing the lower oesophageal sphincter tone thus reducing the possibility of oesophageal reflux in patients immobilized in the recumbent position after operation. Such a regime ought to include the consideration of the use of antacids, metoclopramide, H_2-receptor antagonists and an appropriate diet (Fisher and Cohen, 1978).

REFERENCES

Bartlett, J. G., and Gorbach, S. L. (1975). Critical review. The triple threat of aspiration pneumonia. *Chest*, **68**, 560.

Beischer, N. A., and Mackay, E. V. (1978). *Obstetrics and the Newborn*, 1st edn, p. 370. London: W. B. Saunders and Company.

Blouw, R., Scatliff, J., Craig, D. B., and Palahniuk, R. J. (1976). Gastric volume and pH in postpartum patients. *Anesthesiology*, **45**, 456.

Clark, M. M. (1963). Aspiration of stomach contents in a conscious patient. A case report. *Br. J. Anaesth.*, **35**, 133.

Fisher, R. S., and Cohen, S. (1978). Gastroesophageal reflux. *Med. Clin. N. Am.*, **62**, 3.

Geer, R. T., Lawrence, R. S., Barnes, C. W., Leatherman, J. L., and Marshall, B. E. (1976). Effects of albumin and/or furosemide therapy on pulmonary edema induced by hydrochloric acid aspiration in rabbits. *J. Trauma*, **16**, 788.

Hall, A. W., Moosa, A. R., Clark, J., Cooley, G. R., and Skinner, D. B. (1975). The effects of premedication drugs on the lower oesophageal high pressure zone and reflux status of Rhesus monkeys and man. *Gut*, **16**, 347.

Keats, A. S., Telford, J., and Kurosu, Y. (1957). Studies of analgesic drugs: dihydrocodeine. *J. Pharmacol. Exp. Ther.*, **120**, 354.

Rennie, A. L., Richard, J. A., Milne, M. K., and Dalrymple, D. J. (1979). Postpartum sterilisation—an anaesthetic hazard? *Anaesthesia*, **34**, 267.

UN CAS INHABITUEL DE SYNDROME DE MENDELSON

RESUME

Une malade ayant aspiré de la soupe 36 h après son accouchement a développé un syndrome de Mendelson et y a survécu. Elle était petite et grassouillette, et avait été immobilisée au lit pendant plus longtemps que d'habitude du fait d'une ponction durale effectuée par inadvertance. On pense que ces facteurs l'ont prédisposée à cet accident.

EIN UNGEWÖHNLICHER FALL VON MENDELSONS SYNDROM

ZUSAMMENFASSUNG

Eine Patientin, die 36 Stunden nach der Geburt Suppe eingeatmet hatte, entwickelte Mendelsons Syndrom, blieb aber am Leben. Sie war klein und dick und blieb länger als gewohnlich ans Bett gefesselt, weil sie einen duralen Durchbruch erlitten hatte; diese Faktoren dürften zu dem Unfall beigetragen haben.

UN CASO EXCEPCIONAL DE SINDROME DE MENDELSON

SUMARIO

Una paciente aspiró sopa 36 h después del parto y padeció del síndrome de Mendelson aunque sobreviviera. Era gorda y pequeña y estuvo inmovilizada en cama durante más tiempo que lo normal a raíz de una punción dural errónea; se estima que dichos factores fueron propensos al accidente.

Br. J. Anaesth. (1980), **52**, 461

CALIBRATION OF SOME WRIGHT PEAK FLOW METERS

J. FISHER AND A. SHAW

SUMMARY

The performance of Wright peak flow meters is described using an absolute and precise calibration method. This showed errors as great as 25% with the peak flow meter and 40% with the mini peak flow meter. At large flow rates errors were less. The expected variation between individual peak flow meters was about 12%. The expected variation between individual mini peak flow meters was between 16% and 22%, depending on flow rate.

In both its original (Wright and McKerrow, 1959) and restyled form the Wright peak flow meter (p.f.m.) is widely accepted for measurement of peak expiratory flow rate. Recently a smaller, lower-cost device, the mini p.f.m., has been introduced (Wright, 1978).

Two calibration methods have been used to check the various designs of p.f.m. Steady air flows have been blown through a flow meter connected in series with the meter. This method does not test the response of the p.f.m. to non-steady airflows. Also, it depends on a flow meter which cannot readily be checked for its absolute precision. The other method compares readings from the meter with those obtained from a pneumotachograph for a single group of people. This presupposes the pneumotachograph to be properly calibrated. More important, it is imprecise because subjects do not always produce the same peak flow. In a recent report (Perks et al., 1979) the scatter of results was considerable, particularly at low flows.

Because of these deficiencies, we developed a calibration procedure which can be cross-checked independently. We report our findings for the three types of Wright p.f.m.: the original p.f.m., the restyled p.f.m. and the mini p.f.m.

MATERIALS AND METHODS

A technical description and appraisal of our calibration procedure has been reported elsewhere (Shaw, Fisher and Hughes, 1979). A heavy piston is allowed to fall under gravity in a cylinder. Air is expelled from the lower end of the cylinder to the instrument being calibrated. Sharp-edged orifices manufactured to British Standard 1042 are installed in the cylinder above the piston. These orifices control the acceleration of the piston until a constant velocity and therefore a steady flow has been reached. Various sizes of orifice are used to generate particular peak flows. The flow is checked independently by a timing unit which measures the velocity of the piston during its descent.

Three original p.f.m., 10 restyled p.f.m. and six mini p.f.m. were tested in the survey. Four of the mini p.f.m. had repositioned scales as recommended by Wright (1978) and Perks and others (1979). All meters had been in use in hospitals in the West of Scotland, except two mini p.f.m. (A and C) which were assessed immediately after purchase. There had been no apparent abuse to any meters. Two restyled p.f.m. had just been calibrated by the manufacturer. Ten different peak flows were produced and measured for each p.f.m. Each peak flow was reproduced three times. The dynamic characteristic of every meter was determined by progressively shortening the period of time at which the peak flow rate was maintained. This was done by stopping the piston of the calibrator before it had completed its full stroke. It has been suggested that maintaining a peak flow for 10 ms was sufficient for the original p.f.m. to respond accurately (Wright and McKerrow, 1959).

The pressure loss across each meter was measured using a differential pressure transducer (Elema Schonander E.M.T. 32). Care was taken to avoid air leakage between the calibrator and meter.

RESULTS

The measured peak flows were compared with the readings on each meter. Percentage errors rather

---

J. FISHER, B.SC.; A. SHAW, B.SC., C.ENG.; West of Scotland Health Boards, Department of Clinical Physics and Bio-Engineering, 11 West Graham Street, Glasgow G4 9LF.
Correspondence to A. S.

0007-0912/80/040461-04 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Percentage errors for the restyled p.f.m.*

Actual flow (litre min^{-1})	Meter number									
	1	2	3	4	5	6	7	8	9	10
120	0	4.0	12	12	13	13	15	16	23	25
175	10	18	16	17	17	23	15	19	23	27
230	13	17	20	18	21	24	15	20	23	26
305	13	13	16	16	19	21	13	19	18	20
334	11	9.0	14	11	14	17	12	15	13	17
395	4.1	4.0	7.9	6.5	10	12	4.5	8.4	7.7	14
445	2.2	2.0	4.5	3.7	4.8	9.0	0.0	5.7	4.4	11
510	−1.0	−2.0	2.3	0.2	2.0	4.3	−3.8	2.1	1.3	9.1
575	−2.8	−6.0	−1.7	−2.7	−0.9	0.5	−4.8	−0.5	−2.1	5.5
730	−8.0	−12	−8.0	−9.3	−8.1	−12	−10	−8.8	−10	−2.7

than absolute values were used. The percentage error was defined as:

$$\% \text{ error} = \frac{(\text{meter reading}) - (\text{actual flow})}{(\text{actual flow})} \times 100$$

Table I shows the per cent error of the restyled p.f.m. Meters 4 and 6 had just been re-calibrated by the manufacturer. Table II shows per cent errors for the mini p.f.m. Meters A, C, D and E had re-positioned scales (Perks et al., 1979).

TABLE II. *Percentage errors for the mini p.f.m.*

Actual flow (litre min^{-1})	Meter number					
	A	B	C	D	E	F
103	7	21	25	25	27	35
155	17	25	36	38	36	39
174	22	24	35	37	33	34
215	22	24	30	34	32	32
254	20	19	26	35	28	27
278	19	18	25	33	28	25
295	18	17	22	33	26	24
354	15	12	19	24	23	20
430	9.2	7.0	13	17	17	13
525	4.5	3.0	7.0	12	10	8.0

Figures 1 and 2 show examples of calibration curves for a single restyled p.f.m. and a single mini p.f.m. There were substantial differences in the errors produced by each meter. From our data for the 10 restyled p.f.m. and six mini p.f.m., predicted 95% confidence limits were established. Figure 1 shows our predicted upper and lower limits for restyled p.f.m. and figure 2 similar data for the mini p.f.m. If our sample batch of each type of meter is typical of all meters presently in use, 95 out of 100 instruments would fall within these bands.

Reducing the period at which peak flow was maintained showed that at 30 ms the meter readings were reduced by about 5%. The pressure loss across the various meters at 400 litre min^{-1} was about 15 cm H_2O for the mini p.f.m. and 5 cm H_2O for the restyled and original p.f.m.

DISCUSSION

Our calibrator produces peak flows the values of which are known to an accuracy better than 1.0%. Repeatability of a particular peak flow based on 30 measurements is better than 0.28% (Shaw, Fisher and Hughes, 1979).

Tables I and II show that there are substantial errors in the meter readings for the restyled and mini p.f.m., especially at the lower end of the flow range. Percentage errors for the three original p.f.m. tested tended to be smaller than for the restyled p.f.m., but the pattern of errors was similar: per cent error was positive at slow flow rates and negative at greater flow rates.

The tables show the wide variation in errors between individual restyled and mini p.f.m.

Figure 1 shows that there is a specific calibration curve for the single meter illustrated (no. 3 in table I). For clarity, curves for the other meters are not shown, but they have similar profiles and are an equally good fit. The predicted confidence limits for all restyled meters shown in figure 1 depend upon our sample batch being typical of all instruments in use. Since our instruments were obtained from a wide variety of sources this assumption is reasonable. The calibration curves for two of the original p.f.m. were less than the 95% confidence limits for the restyled p.f.m. This suggests a change in the calibration of the p.f.m. when it was restyled. Curiously, two restyled

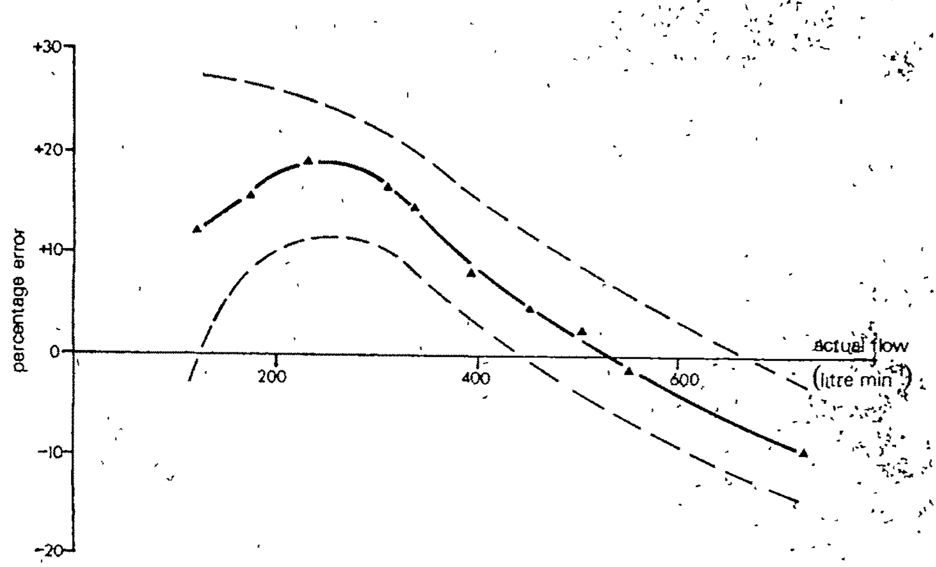


FIG. 1. Percentage errors for a restyled p.f.m. Dotted lines show 95% confidence limits for all the restyled p.f.m. tested.

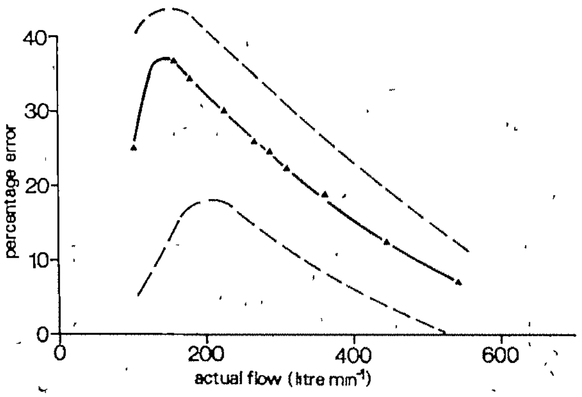


FIG. 2. Percentage errors for a mini p.f.m. Dotted lines show 95% confidence limits for all the mini p.f.m. tested.

p.f.m. with consecutive serial numbers (meters 4 and 5) had very similar characteristics. It is possible that the sample variation is reduced considerably if several instruments are bought at the same time.

Figure 2 also shows a non-linear relationship between per cent error and flow for the mini p.f.m. The typical calibration curve shown is for meter C. Similar shaped curves are produced for the other meters from the data in table II. The 95% confidence limits show a big variation between the individual mini p.f.m. The characteristic variation is much greater than that found by Perks and others (1979). It is obvious from figure 2 that it is inappropriate to use a straight-line regression analysis or to change the calibration simply by repositioning the scale (Wright, 1978; Perks et al., 1979).

The original meter was expected to measure accurately peak flows of duration 10 ms or more. Our findings are that meter readings begin to be affected at a duration of about 30 ms. This dynamic response is sufficiently good to measure peak flow in most subjects.

From our findings several conclusions can be reached. For the restyled p.f.m. it is reasonable to compare results taken on different meters. Our predicted 95% confidence band is about 12% for flows greater than 300 litre min^{-1}. At slower flows the characteristics of the individual p.f.m. may have an increasing effect on the results.

We would not recommend comparing peak flows measured on different mini p.f.m. at flow rates less than about 400 litre min^{-1}.

The absolute calibration of both designs of meter could be improved by alterations to the scale. Both designs of meter would require a new non-linear scale. This would not reduce the variation between individual meters.

A unique calibration graph can be produced for every meter. In this way it is possible to correct the indicated reading, thus obtaining a highly accurate measurement of the actual peak flow generated. However, the mini p.f.m. is a greater resistance meter than is the restyled meter so, even with such corrections, the peak expiratory flows obtained should not be compared directly.

REFERENCES

British Standard 1042. *Methods for the Measurement of Fluid Flow in Pipes. Part* 1. *Orifice Plates, Nozzles and Venturi Tubes.*

Perks, W. H., Tams, I. P., Thompson, D. A., and Prowse, K. (1979). An evaluation of the mini-Wright peak flow meter. *Thorax*, **34**, 79.

Shaw, A., Fisher, J., and Hughes, D. W. (1979). A flow and volume calibrator for respiratory measuring equipment. *J. Med. Eng. Technol.*, **3**, 248.

Wright, B. M. (1978). A miniature Wright peak flow meter. *Br. Med. J.*, **2**, 1627.

—— McKerrow, C. B. (1959). Maximum forced expiratory flow rate as a measure of ventilatory capacity. *Br. Med. J.*, **2**, 1041.

ETALONNAGE DE CERTAINS DEBITMETRES A MAXIMA DE WRIGHT

RESUME

On décrit dans cet article les performances de certains débitmètres à maxima de Wright, mesurées à l'aide d'une méthode d'étalonnage précise et absolue. Celle-ci a fait ressortir des erreurs aussi importantes que 25% dans le cas du débitmètre à maxima, et 40% dans le cas du mini débitmètre à maxima. A des débits élevés, les erreurs ont été moins importantes. Les variations auxquelles on s'attendait entre les divers débitmètres à maxima étaient de l'ordre de 12%. Les variations attendues des divers mini débitmètres à maxima se situaient entre 16% et 22%, suivant le débit.

KALIBRIERUNG EINIGER WRIGHT-SPITZENDURCHFLUSSMESSER

ZUSAMMENFASSUNG

Die Leistung von Wright-Spitzendurchflussmessern wird mittels einer absoluten und präzisen Kalibrierungsmethode beschrieben. Dabei zeigten sich Fehler bis zu 25% mit Spitzendurchflussmessern, und bis zu 40% mit dem Mini-Spitzendurchflussmesser. Bei grossen Durchflussraten waren die Fehler geringer. Die erwarteten Variationen zwischen einzelnen Spitzendurchflussmessern betrugen etwa 12%. Die erwarteten Variationen zwischen einzelnen Mini-Spitzendurchflussmessern betrugen zwischen 16% und 22%, je nach der Durchflussrate.

CALIBRACION DE ALGUNOS CONTOMETROS WRIGHT DE APICE

SUMARIO

Se da una reseña del funcionamiento de los contómetros de ápice Wright al usar un méthodo de calibración preciso y absoluto. Este puso de manifiesto errores de hasta 25% del contómetro de ápice y hasta 40% del mini-contómetro de ápice. Con ritmos de flujo mayores, los errores eran menores. La variación anticipada entre los contómetros de ápice individuales era de alrededor del 12%. La variación anticipada entre los mini-contómetros de ápice se ubicaba entre el 16 y el 22%, según el ritmo del flujo.

Br. J. Anaesth. (1980), **52**, 465

CORRESPONDENCE

PROGRAMMABLE CALCULATOR

Sir,—Dr Kenny (1979) advocates the use of a programmable calculator for computing cardio–ventilatory parameters in respiratory therapy. We are rather surprised by the ease with which he proposes to apply the derived data in clinical practice. There are two main criticisms of the program. First, the procedure for converting oxygen partial pressure into haemoglobin saturation is of little or no value if not corrected for additional shifts of the dissociation curve, such as caused by altered 2,3-DPG activity of the red blood cells. In fact, one may wonder why Dr Kenny takes the trouble to calculate the oxygen saturation at all, as the Radiometer ABL 2 calculates this already, together with the blood-gas values, in the same unreliable way.

Second, the practical value of the calculated data depends not so much on the accuracy of computation as on the accuracy of the underlying clinical measurements.

As a result of the complex mathematical relations involved, small errors in measurement may be considerably magnified by the computation. It is our experience that the calculated data that Dr Kenny proposes are only a rough estimation, and we would not recommend them to play an important role in clinical therapy.

Another point is that the choice of a pocket calculator for processing a rather large number of data (the input of nine variables and the output of 12) seems to be impractical. Nowadays there are several FORTRAN computer programs available for computing respiratory data. It is not too difficult to convert FORTRAN sub-routines to BASIC. At the moment several cheap microprocessor-based systems—so called "personal computers" with BASIC interpreters—are available; anyone who can afford one may try the practical value of these programs.

We are studying some BASIC programs which, amongst other facilities, compute the P_{50} of the blood, convert oxygen and carbon dioxide partial pressures to content and *vice versa*, and estimate the true ideal gas-point as needed for proper calculation of physiological shunt and alveolar deadspace.

T. PORCELIJN
P. C. W. VAN DE BERG
Amsterdam, The Netherlands

REFERENCE

Kenny, G. N. C. (1979). Programmable calculator: a program for use in the Intensive Care Unit. *Br. J. Anaesth.*, **51**, 793.

Sir,—While writing a program for a TI 59 programmable calculator, it has come to our attention that the equation for determining the haemoglobin saturation (Kenny, 1979) is incorrect.

Rather than "$n = Pa_{O_2,corr}$," Thomas (1972) states that:

$$So_2 = (n^4+An^3+Bn^2+Cn)/(n^4+An^3+Dn^2+En+F)$$

where

$n = -Pa_{O_2,corr}$; $A = 15$; $B = 2.045\times10^3$; $C = -2\times10^3$; $D = 2.4\times10^3$; $E = 3.11\times10^4$ and $F = 2.4\times10^6$.

J. R. BISHKO
J. P. JOHNSTON
Gainesville, Georgia, U.S.A.

REFERENCES

Kenny, G. N. C. (1979), Programmable calculator: a programme for use in the Intensive Care Unit. *Br. J. Anaesth.*, **51**, 793.

Thomas, L. J. (1972). Algorithms for selected blood acid–base and blood-gas calculations. *J. Appl. Physiol.*, **33**, 154.

Sir,—Prompted by the interesting article by Dr Kenny (1979), may I offer some comments? I might suggest four small corrections, the first being for the equations on p. 795, which contain the value of $(Pa_{O_2}-Pv_{O_2})$. I believe that this should read $(Ca_{O_2}-Cv_{O_2})$ (Benatar et al., 1973). Second, for the calculation of the virtual shunt, 2.23 mmol litre^{-1} might be taken for $(Ca_{O_2}-C\dot{v}_{O_2})$, since all oxygen content values are calculated in S.I. units. Third, in discussing the method to determine FI_{O_2} to obtain a particular Pa_{O_2}, the article states: "Entry into the program of $Pa_{O_2,new}$ . . . allows calculation . . . of $Cc'_{O_2,new}$." In my opinion, $Ca_{O_2,new}$ is obtained at this stage, from which $Cc'_{O_2,new}$ is then derived and $Pc'_{O_2,new}$ found by using iterative loops in the program. Finally, the equation yielding FI_{O} would be correct when it read:

$$FI_{O_2} = \frac{PA_{O_2}+(Pa_{CO_2}/0.8)}{P_{bar}-47-Pa_{CO_2}+(Pa_{CO_2}/0.8)}$$

PHILIPPE R. HOUSMANS
Antwerp, Belgium

REFERENCES

Benatar, S. R., Hewlett, A. M., and Nunn, J. F. (1973). The use of iso-shunt lines for control of oxygen therapy. *Br. J. Anaesth.*, **45**, 711.

Kenny, G. N. C. (1979). Programmable calculator: a program for use in the Intensive Care Unit. *Br. J. Anaesth.*, **51**, 793.

Sir,—Doctors Porcelijn and van de Berg question the value of deriving the saturation of haemoglobin from the oxygen partial pressure if no correction is made for variations in the red cell concentration of 2,3-DPG. The position of the oxyhaemoglobin dissociation curve is affected by the hydrogen ion concentration, PCO$_2$, 2,3-DPG and other phosphate ester concentrations, and temperature. The ability to correct the position of the curve from a knowledge of all these factors would be ideal, but the question is whether clinically useful information can be derived without a knowledge of the 2,3-DPG concentration within the red cells, since it is not possible at present to measure 2,3-DPG concentrations routinely.

The effects of alteration in therapy on blood Po_2 would be expected to occur within a relatively short period of time. However, changes in the 2,3-DPG concentration take several hours to occur. Thus a calculated change in blood oxygen content as a result of alteration in therapy would be more closely related to a change in blood Po_2 than to a change which had occurred in the 2,3-DPG concentration and would therefore be a useful value to calculate from the Po_2. The equation used in the ABL 2 is less accurate than the Thomas modification of the Kelman equation. An IL 413 blood-gas analyser which cannot calculate the oxygen saturation of blood is also used on some occasions and so the ability to calculate oxygen saturation from blood Po_2 is required.

Errors in measurement affect the results of any calculation; however, three blood samples are usually measured separately and by using the same blood-gas analyser, the trend of changes should be relatively accurate. The principal virtue of the programmable calculator is its low cost, but with the introduction of microprocessor-based computers which can display text on a screen, entry of data following prompt statements is greatly facilitated. However, these are three to four times as expensive as the calculator and may be outside the budget of some intensive care units. Also they were not readily available in this country when the program was being prepared.

A major advantage of any such system is the ease with which improvements and modifications can be made to the original program. If routine measurement of 2,3-DPG concentration becomes possible, a correction factor can be incorporated into the present program.

I thank Drs Bishko, Johnston and Housmans for pointing out errors which had not been noticed during the presentation of the manuscript. The third point made by Dr Housmans is quite correct in that $Cc'_{O_2\text{new}}$ is derived from the calculated $Ca_{O_2\text{new}}$. This should have been stated in the article, rather than merely implied.

GAVIN N. C. KENNY
Glasgow

2-CHLOROPROCAINE COMBINED WITH BUPIVACAINE

Sir,—Sometimes regional anaesthesia is effected by combining drugs with rapid and slow onsets, for example 2-chloroprocaine and bupivacaine. We do not know if the components of the mixture act independently, additively or synergistically. The writer has determined duration of anaesthesia in rats utilizing bilateral coccygeal nerve blocks with the following mixtures:

I 3% 2-chloroprocaine 0.4 ml + normal saline 0.4 ml
II 3% 2-chloroprocaine 0.4 ml + bupivacaine 0.75% 0.4 ml
III 0.75% bupivacaine 0.4 ml + normal saline 0.4 ml
IV 0.75% bupivacaine 0.4 ml (included for comparison).

The response to repetitive electrical stimulation of the rat's tail indicated the duration of anaesthesia. The results are shown in figure 1. Because a nerve stimulator was used to locate the coccygeal nerves the animals were immobilized briefly under methoxyflurane anaesthesia. Thus onset time of the block could not be determined.

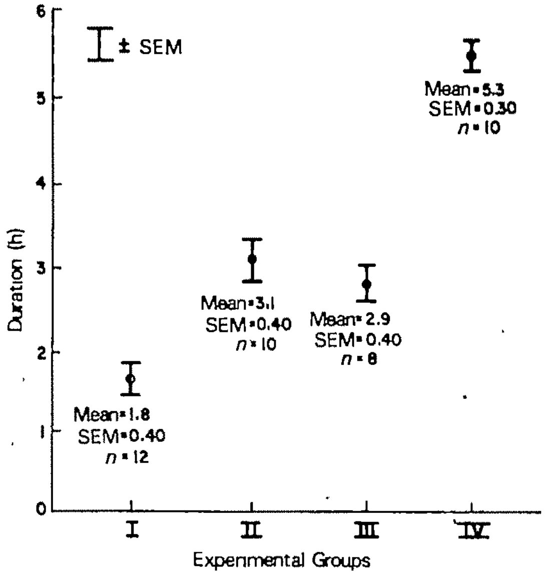


FIG. 1. Duration of anaesthesia in each group.

It is apparent that the combined local anaesthetics act neither additively nor synergistically; the duration for the 2-chloroprocaine–bupivacaine mixture is similar to that of bupivacaine–normal saline. The 2-chloroprocaine does, however, decrease the duration of anaesthesia for bupivacaine, probably diluting the mixture and reducing the concentration of bupivacaine.

The utilization of local anaesthetic mixtures has proved clinically advantageous by reducing the onset time. Nevertheless, it appears to shorten the duration of anaesthesia even if, in most instances, the reduction is not clinically significant.

RICHARD M. ROSENBLATT
California, U.S.A.

HUMIDIFICATION IN ANAESTHESIA

Sir, I would like to comment on the criticism by Dr Chalon (1979) of the Editorial on Humidification (Hayes, 1979). The 12 references quoted by Dr Hayes are taken from eight different publications from five different countries on three continents, yet Dr Chalon makes the accusation of insularity and extends it to include all British anaesthetists. I believe Dr Chalon could find greater parochialism closer to home.

If he feels that the last line of the editorial (asking for further study) has long been answered on many occasions by the 250 or so publications he claims to have read, clearly the authors of these articles are not so easily satisfied as is Dr Chalon that all requiring to be known on the subject is known.

D. E. JEAL
Hershey, Pennsylvania, U.S.A.

REFERENCES

Chalon, J. (1979). Humidification in anaesthesia. *Br. J. Anaesth.*, **51**, 1094.

Hayes, B. (1979). Humidification in anaesthesia. *Br. J. Anaesth.*, **51**, 389.

ANTICHOLINERGIC PREMEDICATION

Sir,—There has been correspondence (Gilmour, 1979; Mirakhur and Dundee, 1979) following the publication of our paper on anticholinergic premedicants (Mirakhur, Dundee and Connolly, 1979).

We have since calculated the data on heart rate on a dose per unit weight basis. Table I shows the correlation coefficients (r values) between changes in heart rate and weight related dose ($\mu g\ kg^{-1}$) at each of the times shown. The positive correlations are significant for both routes of atropine administration from 40 min onwards indicating a greater increase in heart rate when dose per unit weight is increased. The correlation is, however, not good at all times. For i.m. hyocine and glycopyrronium, the correlations are significant only from 60 min onwards, perhaps a reflection of the less significant effects on heart rate of these two drugs (Mirakhur, Dundee and Connolly, 1979 (table II)). The absence of any real correlation for oral administration of these two drugs indicates their inefficient absorption.

We further examined the possibility of any correlation between change in heart rate and weight for each group at each time. Table II shows that this correlation is generally poor and is rarely significant.

R. K. MIRAKHUR
J. W. DUNDEE
J. D. R. CONNOLLY
Belfast

REFERENCES

Gilmour, I. J. (1979). Anticholinergic premedication. *Br. J. Anaesth.*, **51**, 910.

Mirakhur, R. K., and Dundee, J. W. (1979). Anticholinergic premedication. *Br. J. Anaesth.*, **51**, 911.

—— —— Connolly, J. D. R. (1979). Studies of drugs given before anaesthesia. XXVII: Anticholinergic premedicants. *Br. J. Anaesth.*, **51**, 339.

TABLE I. *Correlation coefficients* (r) *between change in heart rate and weight-related dose* ($\mu g\ kg^{-1}$). $^*P < 0.05$

		n	Time (min) 20	40	60	90	Induction
Atropine	I.m.	60	0.244	0.338*	0.606*	0.551*	0.307*
	Oral	60	0.227	0.309*	0.388*	0.343*	0.381*
Hyoscine	I.m.	60	0.068	0.190	0.325*	0.285*	0.459*
	Oral	60	0.127	0.051	−0.122	0.010	0.060
Glycopyrronium	I.m.	60	0.169	0.325	0.610*	0.513*	0.293*
	Oral	60	−0.040	−0.043	−0.032	0.125	0.110

TABLE II. *Correlation coefficients* (r) *between change in heart rate and weight.* $^*P < 0.05$

		Drugs (mg)	n	Time (min) 20	40	60	90	Induction
Atropine	I.m.	0.5	20	0.183	0.357	0.155	0.164	−0.062
		1.0	20	−0.150	−0.334	−0.194	−0.112	−0.253
		2.0	20	−0.218	−0.414	−0.519*	−0.464*	−0.256
	Oral	0.5	20	0.293	0.471*	0.423	0.207	0.141
		1.0	20	0.098	0.198	0.060	0.139	−0.273
		2.0	20	0.229	0.181	0.303	0.062	−0.337
Hyoscine	I.m.	0.25	20	0.135	0.010	0.325	0.307	0.022
		0.5	20	−0.056	0.074	0.054	0.136	−0.063
		1.0	20	0.032	0.031	−0.359	−0.076	−0.161
	Oral	0.25	20	−0.068	0.158	−0.126	−0.084	−0.214
		0.5	20	0.107	−0.053	0.010	0.098	0.053
		1.0	20	0.392	0.305	0.617*	0.730*	−0.145
Glycopyrronium	I.m.	0.1	20	0.164	0.184	−0.090	−0.044	−0.389
		0.2	20	−0.248	−0.372	−0.398	−0.191	0.345
		0.4	20	−0.223	−0.154	−0.240	−0.281	−0.304
	Oral	2.0	20	0.263	−0.221	−0.467*	−0.578*	−0.029
		4.0	20	−0.179	−0.252	−0.430	−0.442	0.011
		8.0	20	−0.108	−0.319	−0.059	−0.245	0.331
Placebo			20	−0.171	−0.090	−0.170	0.035	0.025

Br. J. Anaesth. (1980), 52, 468

BOOK REVIEWS

Medical Management of the Critically Ill. Edited by G. Hanson and P. L. Wright. Published by Academic Press. Pp. 1050; illustrated; indexed. Price £45.00; $93.25.

This is a useful reference book for the non-specialist worker in intensive care. It should be of particular value in the district hospital setting, when the case load may be quite variable both in numbers, in range of clinical problems, and where there is frequent rotation of medical staff. Under these circumstances it is probable that no individual will be sufficiently experienced to cope immediately with every clinical condition in the I.T.U. This book fills the need for a clearly written account of the diagnosis and management of the vast majority of disorders encountered.

The editors come from a centre well known for its expertise in intensive therapy; contributions have been made not only from the staff at Whipps Cross Hospital, but also by numerous nationally known experts from other centres in the United Kingdom and one Australian centre. In all there are 38 contributors, but a major part of the writing is by Dr Gillian Hanson, who has contributed no less than 22 chapters. The book succeeds in its aim to describe the management of problems generally encountered in an I.T.U. serving a General Hospital. It is conveniently divided into four parts: management of general problems arising during treatment of a specific illness; treatment of specific aspects of acute illness; ancillary facilities required for an I.T.U.; and information for those setting up an I.T.U.

A useful glossary of terms appears with which the reader may begin to participate in the form of "Medspeak" often used in contemporary I.T.U. practice. However, the glossary employs a random use of punctuation and of abbreviation. Chemical names appear with no punctuation, e.g. ATP, CPK, G-6-PD, or full punctuation, e.g. 2,3 D.P.G., V.M.A., D.T.P.A. Respiratory abbreviations have long been standardized, so why re-invent D.L.C.O. when D_LCO is the well-established abbreviation and why not R_{aw} rather than R for airways resistance?

One of the problems in the reviewer's intensive therapy unit is tabulating data from each patient so that the information can be readily used in making decisions. Most units have designed their own data sheet. Is this because intensive care doctors are such individualists that every unit must inevitably have a different system? In my view non-specialized units are quite likely to have similar clinical problems, and I would have welcomed a chapter on the methods and standardization of data recording. The mini computer seems to provide the answer in the near futuer, but J. P. Blackburn pointed out that his experience with computers in the I.T.U. had, until now, been disappointing. Perhaps he should have made a clearer distinction between continuous monitoring of data such as e.c.g. and vascular pressures and the intermittent recording and display of haematological, biochemical, fluid balance and other data.

The sections on specific and general problems of management are excellent, but the use of vasodilators in the management of cardiogenic shock might usefully have been expanded in the section on cardiac care. If the editors limited discussion of this subject because they thought that the Swan–Ganz catheter and pressure transducer are facilities denied to the I.T.U. in most district hospitals, then why include details on the technique of pulmonary embolectomy requiring cardiopulmonary bypass? The use of barbiturates in reducing post-hypoxic brain damage is still *sub judice*, but the subject deserves some discussion and suggestion of dose regimen. Mechanical ventilation of the lungs of patients with severe non-homogeneous alveolar pathology is often one of the most difficult management problems in the I.T.U. After many discussions with Professor John Robinson, who contributed the chapter on Respiratory Care, I remain unconvinced that varying the wave-forms of pressure and flow is important in the management of these patients. He may be right, but I am not sure that the evidence so far available on the efficacy of different wave forms in parenchymal lung disease supports his point of view. Perhaps the current interest in high frequency (15 Hz) ventilation will give a new dimension to our debate?

The book is marred by a number of typographical errors, including the old chestnut "military" tuberculosis and the figure on p. 949 is upside down. Although a very expensive volume, it is nevertheless full of good things and is a "must" for every intensive care unit.

J. G. Jones

Practical Dental Anaesthesia. By A. Kilpatrick. Published by Churchill Davidson. Pp. 72; illustrated; indexed. Price £3.50.

This book is a personal account of the author's techniques and practice of dental anaesthesia as developed over the past 20 years. Also included are chapters on complications, inhalation sedation, apparatus and the economics of the specialty.

This book will be read with interest by those already practising dental anaesthesia or undergoing anaesthetic training, and with profit by established anaesthetists who are contemplating entering such practice. Regrettably, it cannot be recommended as a first text for undergraduate dental students.

D. P. Braid

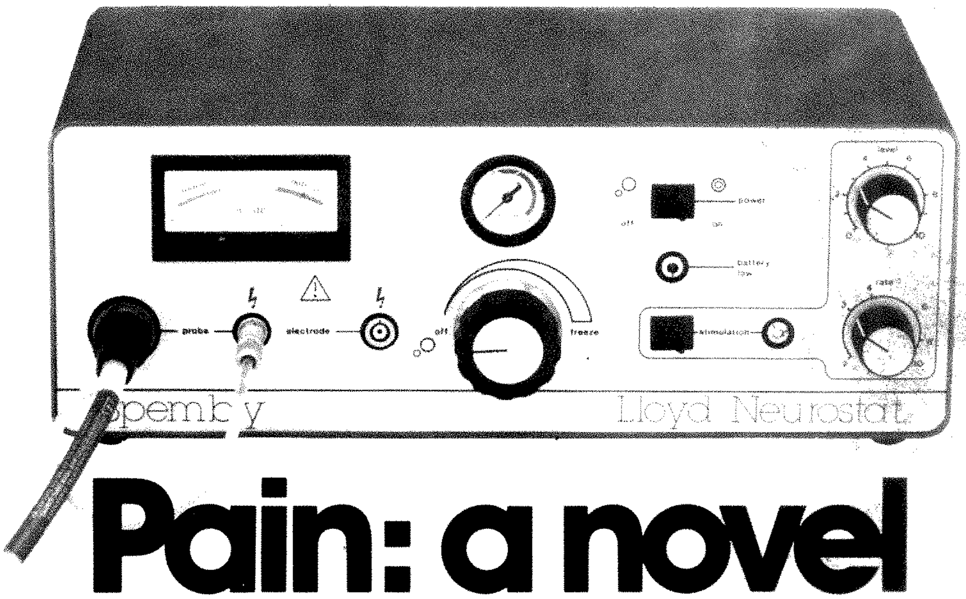
Clinical and Resuscitative Data, 2nd edn. Edited by R. P. H. Dunnill, M. P. Colvin and B. E. Crawley. Published by Blackwell Scientific Publications. Pp. 185; illustrated; indexed. Price £5.80.

This excellent pocket-book full of information designed particularly for the anaesthetist and the resuscitationist has reached its second edition. The deserved popularity of the first edition is likely to be assured for this successor both for its value in the emergency setting and the interest with which a few moments of browsing can be rewarded.

Alastair A. Spence

Printed in Great Britain by John Wright and Sons Ltd at The Stonebridge Press, Bristol BS4 5NU

© Macmillan Journals Ltd 1980



Pain: a novel approach...

The revolutionary Lloyd-Neurostat. A major breakthrough in the treatment of intractable, acute and chronic pain from Spembly.

Spembly have used their unequalled experience in cryosurgery to develop a system which locates and freezes peripheral nerves, giving a long-term reversible block with low incidence of neuroma and neuritis.

The technique is called cryoanalgesia, and clinical research is constantly exploring new applications.

Another form of non-drug treatment is the Spembly 9000, a highly effective TENS system.

TENS provides a low-risk, non-invasive technique for symptomatic relief of pain of many different etiologies

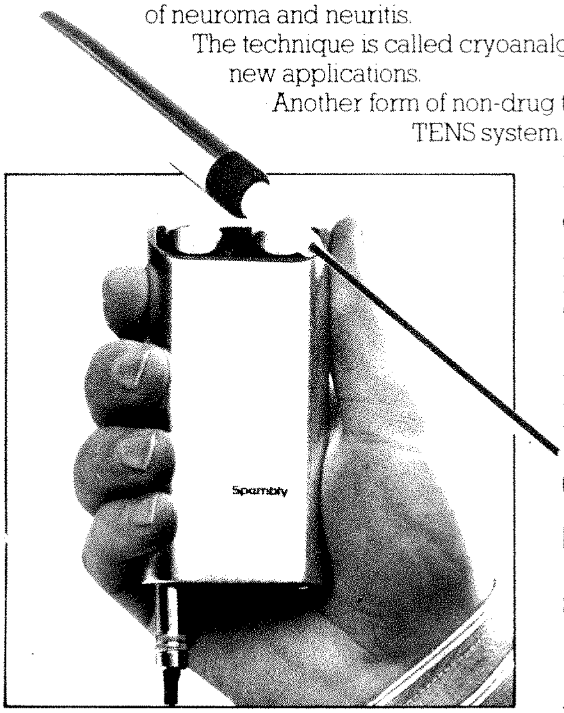
A combination of advanced specification and high performance at economic cost make the 9000 range one of the finest available.

For further information on Spembly products phone Andover 65741.

And get the facts from Mike Alderson.

Spembly

Spembly Limited
Newbury Road Andover Hampshire [illegible]
telephone (0264) 65741 telex 4740[illegible]



BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 4 *Published monthly* APRIL 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27.50, Airmail £50 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

---

CONTENTS

PAGE

EDITORIAL: Steroid anaesthesia 363
C. Prys-Roberts and J. Sear

EXPERIMENTAL

Antagonism of ketamine–diazepam anaesthesia by 4-aminopyridine in human volunteers 367
S. Agoston, P. J. Salt, W. Erdmann, T. Hilkemeijer, A. Bencini and D. Langrehr

Effect of ketamine on transmission in sympathetic ganglia 371
V. Mahmoodi, A. J. Byrne, T. E. J. Healy and S. Z. Hussain

Site of the muscle cell abnormality in swine susceptible to malignant hyperpyrexia 377
F. Okumura, B. D. Crocker and M. A. Denborough

Response of MHS swine to i.v. infusion of lignocaine and bupivacaine 385
G. G. Harrison and D. F. Morrell

Half-life of angiotensin II in the conscious and barbiturate-anaesthetized rat 389
B. J. Chapman, D. P. Brooks and K. A. Munday

Functional residual capacity and ventilatory pressures during positive-pressure ventilation at high frequencies 395
A. Jonzon, Z. Rondio and G. Sedin

CLINICAL INVESTIGATION

Artery-to-muscle onset time for neuromuscular blocking drugs 403
B. Minsaas and J. Stovner

Supraclavicular brachial plexus block using a nerve stimulator and an insulated needle 409
I. Yasuda, T. Hirano, T. Ojima, N. Ohhira, T. Kaneko and M. Yamamuro

New anaesthetic formulation for epicutaneous application tested for cutting split skin grafts .. 413
L. Ohlsén and S. Englesson

Comparison of carbonated bupivacaine and bupivacaine hydrochloride for extradural anaesthesia 419
D. T. Brown, D. H. Morison, B. G. Covino and D. B. Scott

PAGE

Placental transfer and neonatal effects of diazepam when administered to women just before delivery 423
C. B. McAllister

Comparison of three benzodiazepines for oral premedication in minor gynaecological surgery .. 429
C. G. Male, Y. T. Lim, M. Male, J. M. Stewart and J. M. Gibbs

Comparison of the subjective effects and plasma concentrations following oral and i.m. administration of flunitrazepam in volunteers 437
R. S. J. Clarke, J. W. Dundee, W. A. W. McGowan and P. J. Howard

Comparison of the subjective effects and plasma concentrations following oral and i.m. administration of flunitrazepam in patients 447
W. A. W. McGowan, J. W. Dundee, R. S. J. Clarke and P. J. Howard

A double-blind comparison between fentanyl and buprenorphine in analgesic-supplemented anaesthesia 453
B. Kay

CASE REPORT

An unusual case of Mendelson's Syndrome .. 459
R. S. Vaughan, G. A. D. Rees and G. L. Williams

APPARATUS

Calibration of some Wright peak flow meters .. 461
J. Fisher and A. Shaw

CORRESPONDENCE

Programmable calculator 465
2-Chloroprocaine combined with bupivacaine .. 465
Humidification in anaesthesia 466
Anticholinergic premedication 467

BOOK REVIEWS

Medical Management of the Critically Ill 468
Practical Dental Anaesthesia 468
Clinical and Resuscitative Data 468

EDITORIAL BOARD page ii

© **SCIENTIFIC & MEDICAL DIVISION, MACMILLAN PUBLISHERS LTD, HOUNDMILLS, BASINGSTOKE, HAMPSHIRE RG21 2XS**

Acc
12.9.8

Volume 52, No. 5 May 1980

British Journal of Anaesthesia

Editor of General Issues: A. A. Spence

The new IVAC 630 Volumetric Infusion Pump is surely accurate and it speaks for itself

With all the safety and accuracy you'd expect from IVAC, the new IVAC 630 is without doubt the most sophisticated infusion pump ever developed.

Its unique micro-computer makes drug and fluid delivery more trouble-free than ever before. It displays a wide variety of messages, from set-up procedures to alarm situations on its easy-to-read display panel. As a result, improper set-up is unlikely and the operator knows at a glance the total volume delivered, the exact flow rate and what problems there are should an alarm situation occur.

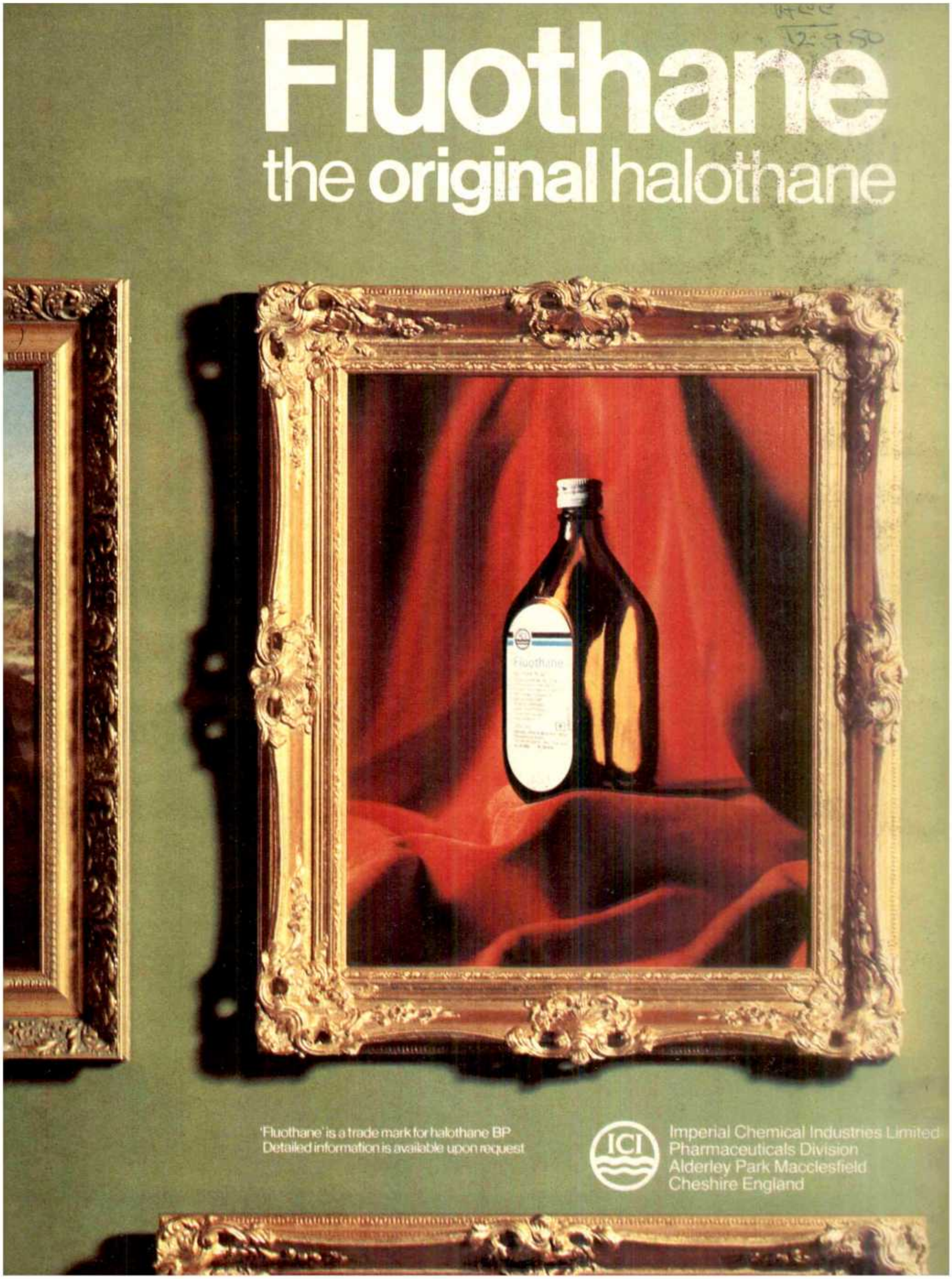
Designed to deliver fluids in a closed system within fine tolerances, the IVAC 630 is ideal for critical infusions requiring very high or very low rates. Furthermore, the volume infused is displayed in 0.1ml increments. So, send today for details about the first infusion pump to actually speak for itself. And let us talk to you.

IVAC

IVAC
IVAC House, Bessborough Road,
Harrow, Middx. HA1 3DT.
Tel: (01) 864 9624. Telex: 8951734.

IVAC 630 Volumetric Infusion Pump

Acc
12.9.80



Fluothane
the original halothane

'Fluothane' is a trade mark for halothane BP
Detailed information is available upon request

ICI
Imperial Chemical Industries Limited
Pharmaceuticals Division
Alderley Park Macclesfield
Cheshire England

EDITORIAL BOARD

Editor of General Issues

A. A. SPENCE, *Reader, University Department of Anaesthesia, Western Infirmary, Glasgow*

Editor of Postgraduate Educational Issues

J. NORMAN, *Professor of Anaesthetics, The General Hospital, Tremona Road, Southampton SO9 4XY*

C. M. CONWAY, *Professor of Anaesthesia, Westminster Hospital, London*
E. A. COOPER, *Professor of Anaesthesia, University of Newcastle upon Tyne; Honorary Consultant Anaesthetist, Newcastle University Hospitals*
J. W. DUNDEE, *Professor of Anaesthesia, Queen's University of Belfast*
F. R. ELLIS, *Reader in Anaesthesia, University of Leeds*
W. FITCH (Assistant Editor), *Senior Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*
G. M. HALL, *Senior Lecturer in Anaesthetics, University of London, Royal Postgraduate Medical School*
C. J. HULL, *Senior Lecturer in Anaesthesia, University of Newcastle*
A. R. HUNTER (Chairman), *Professor of Anaesthesia, University of Manchester*
D. G. MCDOWALL, *Professor of Anaesthesia, University of Leeds*
W. W. MAPLESON, *Professor of the Physics of Anaesthesia, Welsh National School of Medicine, University of Wales*
J. F. NUNN, *Head of Division of Anaesthesia, Clinical Research Centre, Harrow; Honorary Consultant Anaesthetist, Northwick Park Hospital*
J. P. PAYNE, *British Oxygen Research Professor of Anaesthetics, Royal College of Surgeons of England*
C. PRYS-ROBERTS, *Professor of Anaesthetics, University of Bristol*
J. E. RIDING (Hon. Treasurer), *Consultant Anaesthetist, United Liverpool Hospitals; Honorary Lecturer in the Department of Anaesthesia, University of Liverpool*
J. G. ROBSON, C.B.E. *Professor of Anaesthetics, University of London, Royal Postgraduate Medical School*
D. B. SCOTT, *Consultant Anaesthetist, Royal Infirmary, Edinburgh*
G. SMITH, *Professor of Anaesthesia, The General Hospital, Leicester*
M. K. SYKES, *Professor of Clinical Anaesthesia, Royal Postgraduate Medical School, London*

Editorial Assistants

KIRSTEEN M. S. DEWAR, *Consultant Anaesthetist, Western Infirmary, Glasgow*
G. N. C. KENNY, *Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*

Papers for publication and all editorial communications should be addressed to the Editor, University of Glasgow, Department of Anaesthesia, Western Infirmary, Glasgow G11 6NT; business communications to the publishers: Scientific & Medical Division, Macmillan Publishers Ltd, Houndmills, Basingstoke, Hampshire RG21 2XS.
Published monthly. Annual subscriptions: U.K. £22·50, U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27·50, Airmail £50; (or equivalent in any other currency). ISSN 0007–0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.
Overseas subscribers may make payments into U.K. Post Office Giro Account No. 519 2455. Full details must accompany the payment.
Second Class Postage Paid New York, N.Y. U.S. Mailing Agent: Expediters of the Printed Word, Ltd, PO Box 1305, Long Island City, N.Y. 11101.

All enquiries concerning advertising should be addressed to
Advertisement Department, Macmillan Journals Ltd, 3 Dyers Buildings, Holborn, EC1N 2NR (Telephone 01-831 6901). © Copyright: Macmillan Journals Ltd, 1980.
Registered Office: 4 Little Essex Street, London WC2R 3LF

RIPPLE
HEAT
RIPPLE
COOL

It is in the interests of both patient and nursing staff that everything possible is done to avoid pressure sores.

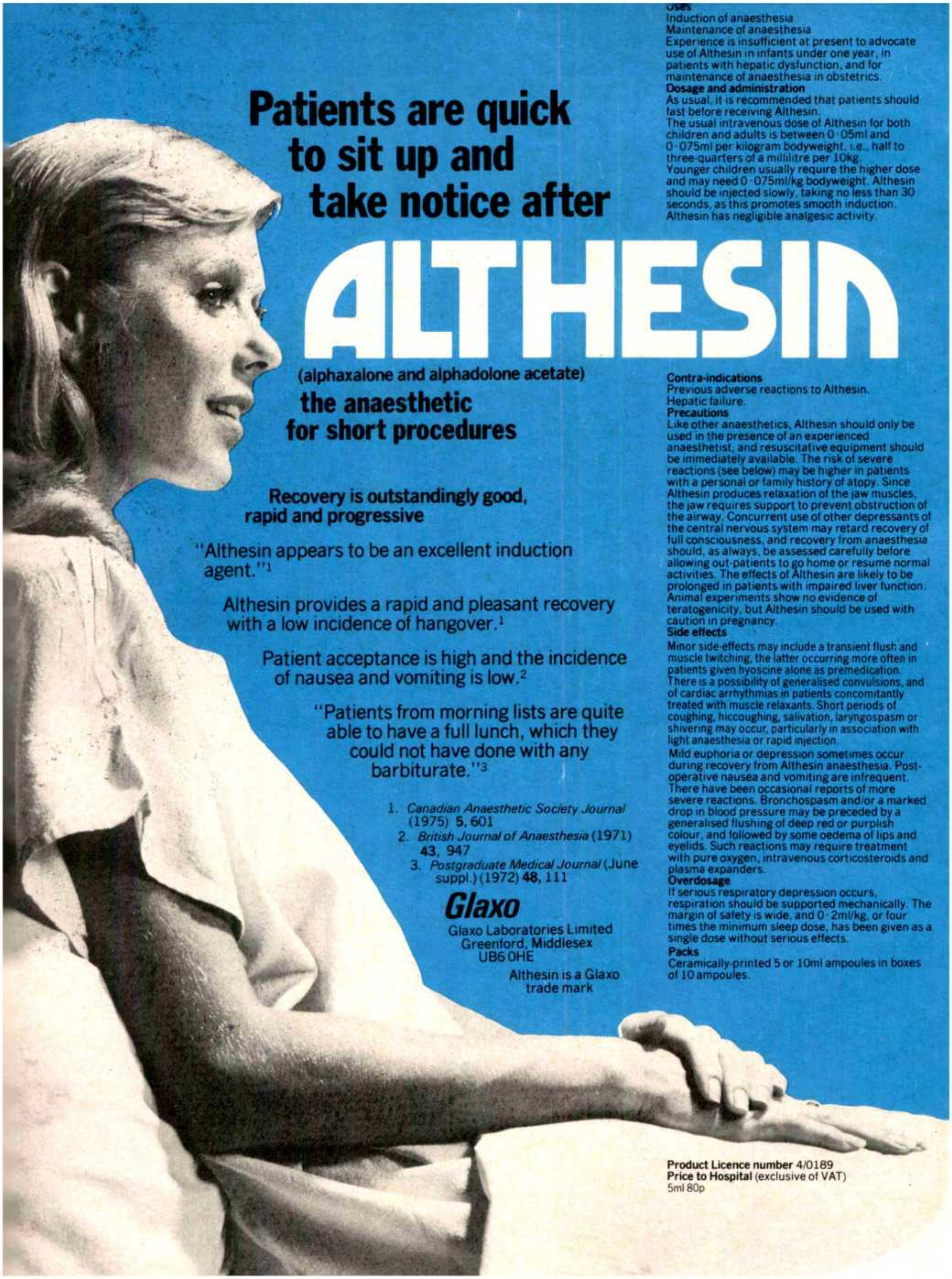
Patients are at their most vulnerable when on the operating table. The Gelman Hawksley Ripple Heat Unit relieves pressure and controls temperature loss, this same unit continues to provide care when the patient returns to the ward.

The Gelman Hawksley Ripple Cool is invaluable when cooling techniques are required. This new unit will heat/cool and ripple while controlling temperature within a range of 10°C to 40°C.

Contact us in Northampton, we will be happy to arrange a demonstration.

GELMAN
HAWKSLEY
LIMITED

UK Sales and Service
10 Harrowden Road, Brackmills
Northampton NN4 0EB
Tel: 0604 65141
Telex: 311871 Gelawk



Patients are quick to sit up and take notice after

ALTHESIN

(alphaxalone and alphadolone acetate)

the anaesthetic for short procedures

Recovery is outstandingly good, rapid and progressive

"Althesin appears to be an excellent induction agent."[1]

Althesin provides a rapid and pleasant recovery with a low incidence of hangover.[1]

Patient acceptance is high and the incidence of nausea and vomiting is low.[2]

"Patients from morning lists are quite able to have a full lunch, which they could not have done with any barbiturate."[3]

1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

Glaxo

Glaxo Laboratories Limited
Greenford, Middlesex
UB6 0HE

Althesin is a Glaxo trade mark

Uses
Induction of anaesthesia
Maintenance of anaesthesia
Experience is insufficient at present to advocate use of Althesin in infants under one year, in patients with hepatic dysfunction, and for maintenance of anaesthesia in obstetrics.

Dosage and administration
As usual, it is recommended that patients should fast before receiving Althesin.
The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e., half to three-quarters of a millilitre per 10kg.
Younger children usually require the higher dose and may need 0·075ml/kg bodyweight. Althesin should be injected slowly, taking no less than 30 seconds, as this promotes smooth induction.
Althesin has negligible analgesic activity.

Contra-indications
Previous adverse reactions to Althesin.
Hepatic failure.

Precautions
Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants of the central nervous system may retard recovery of full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume normal activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects
Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, and of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post-operative nausea and vomiting are infrequent. There have been occasional reports of more severe reactions. Bronchospasm and/or a marked drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids and plasma expanders.

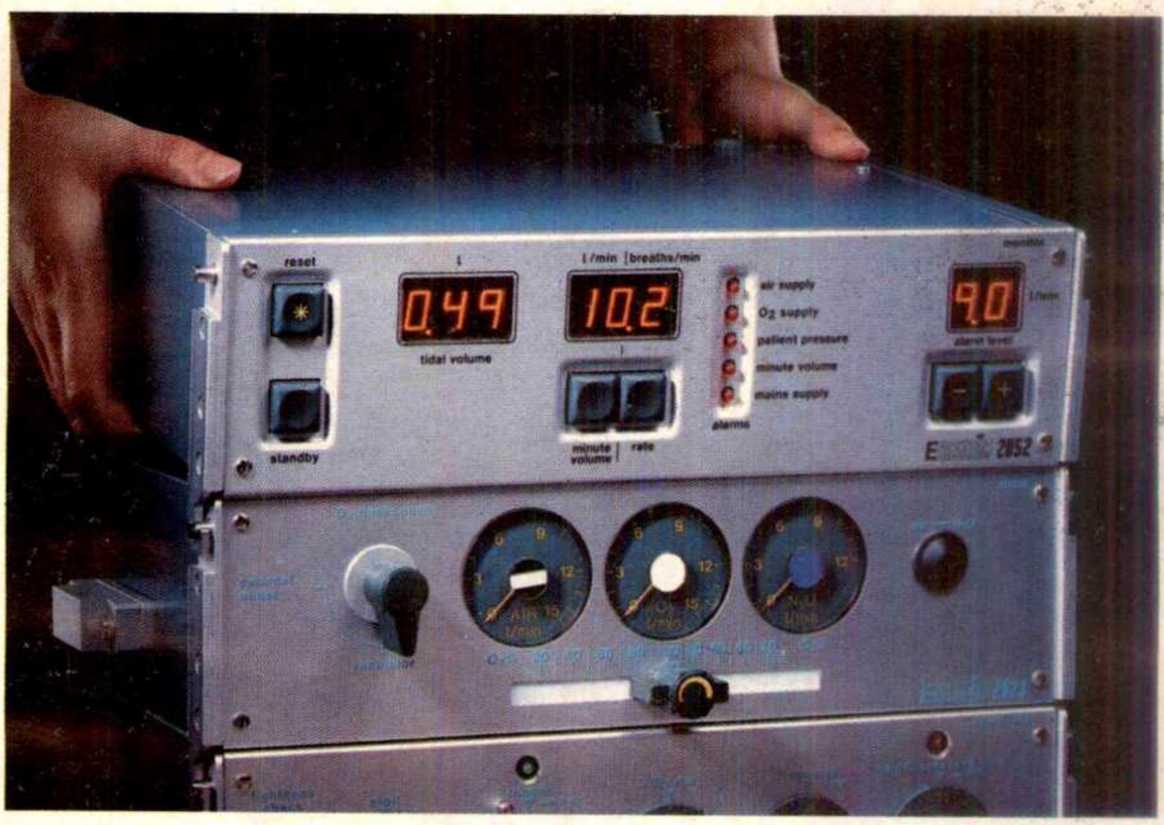
Overdosage
If serious respiratory depression occurs, respiration should be supported mechanically. The margin of safety is wide, and 0·2ml/kg, or four times the minimum sleep dose, has been given as a single dose without serious effects.

Packs
Ceramically-printed 5 or 10ml ampoules in boxes of 10 ampoules.

Product Licence number 4/0189
Price to Hospital (exclusive of VAT)
5ml 80p

The Engström 2000 respirator with a brand new monitoring unit.

It can even print what's happening.



A new microprocessor controlled monitoring unit for the ventilation of the patient gives individual and easily-identified alarms that cover all situations. It gives you a digital display of breath-to-breath tidal volumes, true minute volumes, and the spontaneous or manual breathing rate.

The Engström 2000 is an electronic, modular design. It gives stable settings and has a wide choice of programmed functions, including PEEP, Trigger, Sigh, spontaneous breathing and manual ventilation.

A special feature is the printer output. A standard printer can give you a continuous printout of respiratory parameters and alarm conditions, if they occur. This printout, in plain words, is a unique Engström feature.

Your nearest Engström representative will be glad to give more information, or to arrange a demonstration.

ENGSTRÖM

Engström Medical AB,
Box 1295, S-171 25 Solna, Sweden

Engström 2000 - the respirator with features that puts it ahead of all others.

"Minivent" Ventilator

This low cost, easy to handle, pocket size, portable ventilator produces completely automatic, reliable and efficient ventilation in anaesthesia. It requires no extraneous power source and fits standard continuous flow anaesthetic machines. Precision manufactured in durable materials . . . . Price **£72**

MINIVENT KIT consisting of Minivent, non-return valve with catheter mount, reservoir bag, bag mount to fit Boyle's/British Standard machines—all specially designed for use with the Minivent . . . . Price **£98**

Available on sale or return basis

MINIVENT
(ROOM302
Abbey Life House, 1-3 St. Paul's Churchyard,
London EC4M 8AU (01-248 6724)

British Medical Bulletin
Volume 36 1980

No 1 January
Chemical Carcinogenesis Scientific Editor: P Brookes

No 2 May
The Muscular Dystrophies Scientific Editors: J N Walton & F L Mastaglia

No 3 September
Diagnostic Imaging Scientific Editor: L Kreel

A descriptive leaflet, with an order form, is available from
The British Council
Medical Department, 65 Davies Street, London W1Y 2AA

THE HOWORTH ACTIVE SCAVENGING SYSTEM FOR ANAESTHETIC GAS POLLUTION

This is an active system designed specifically to reduce air pollution by anaesthetic gases to well below the maximum levels recommended by N.I.O.S.H. in the U.S.A. and by the British Association of Anaesthetists in the U.K. The system complies with the principles of D.H.H.S. Circular HC(76)38.

SYSTEM CHARACTERISTICS

High Volume, Low Pressure

The high volume ensures high dilution of gases and all moisture, thus avoiding explosion risk and any condensation within the ducts.

No excessive or dangerous suction pressure can be exerted on the anaesthetic machine circuits.

There is no imbalance of pressure if only one extract point is being used on a multi-point system.

Versatility of Function

This system is applicable to any anaesthetic circuit and any type of ventilator and will cope with extracts from induction rooms, operating rooms and also to exhaust the patient's exhaled breath in recovery rooms with special attachments for dental units and the new Howorth-Great Ormond Street paediatric unit.

Break Point Connections

These are designed to limit the suction pressure on the machine circuits to the required and recommended limit of 0.5 cm/H_2O.

They cannot be occluded accidentally.

They are compatible with 18 mm, 22 mm or 30 mm extract hose and they are capable of exhausting peak flows of up to 300 litres per minute.

Versatility of Layout Design

The system can be adapted to scavenge simultaneously, for example, four anaesthetic machine points, or three or four recovery room points, or combinations of machine and recovery room points.

Each extract point is fitted with a self-closing valve which enables alternative extract points to be installed on the same fan system.

Inbuilt Safety Factors

A failure light on the control and indicating panels is activated by an air flow sensor fitted to the fan.

The fan motor is outside the air stream, and the fan blades are of non-ferrous material.

Should the fan motor fail, the system can still operate, as a temporary measure, as a passive system without adversely affecting the anaesthetic circuits.

Typical Test Results

Hospital 'A'
Operating Theatre—no scavenging: 600–1000 ppm N_2O
passive system: 230–300 ppm N_2O
Howorth system: 0–3 ppm N_2O
Comment: The 3 ppm were traced to leaks in the anaesthetic circuitry.
Hospital 'B'
Operating Theatre—no scavenging: 800–1000 ppm N_2O
Howorth system: 0–6 ppm N_2O
Comment: The 6 ppm were traced to a leaking cuff on the endotracheal tube.

Protected by registered design and patents

HOWORTH SURGICAIR

Lorne Street, Farnworth, Bolton. Tel: 0204-71131 Telex: 635242

Design Council Award 1977

Marcain extends the frontiers of local analgesia

10 AMPOULES OF 10 ml
MARCAIN PLAIN 0.5%
INJECTION
10 AMPOULES OF 10 ml
DF
MARCAIN
PLAIN 0.5%
INJECTION
A long acting local anaesthetic
Each 10 ml ampoule contains
Bupivacaine hydrochloride BP 0.5% w/v

Marcain has been shown to produce a high incidence of successful blocks, rapid onset of action, and remarkably low systemic toxicity when used for intravenous regional analgesia. Please write for a copy of our information leaflet.

LONG-ACTING
Marcain
bupivacaine hydrochloride BP
DF

The Trade Mark "MARCAIN" is the property of Aktiebolaget Bofors, Sweden.
DUNCAN FLOCKHART & CO. LIMITED, LONDON E2 6LA.
Further information is available on request.

The choice is yours with the

PORTEX EPIDURAL SYSTEM

The most advanced design of Epidural Cannula* - smooth, flexible, kink-resistant, with excellent flow rates.

The Epidural Minipack - complete with the Portex Epidural Cannula** and thin-wall, single-use Tuohy needle - safe and economical with no costly extras.

The Portex Epidural Filter to complete the system, offering an effective bacterial and particulate barrier.

* Cannula supplied sterile in 16G and 18G, in radio-opaque or clear nylon. Option of 16G clear Cannula with open end.

** Minipack supplied sterile in 16G and 18G. Choice of radio-opaque or clear nylon Cannula.

For further details contact:

PORTEX LIMITED,
HYTHE, KENT, ENGLAND, CT21 6JL.
Tel: 66863 / 60551 Telex 96165

PORTEX S.A.,
ZI. de la VIGOGNE
62600 BERCK-SUR-MER,
FRANCE. Tel: (21) 090582

PORTEX

GUIDE TO CONTRIBUTORS

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. Two issues each year deal mainly with material of postgraduate educational value.

PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publishers.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted.

LEGAL CONSIDERATIONS

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

PREPARATION OF MANUSCRIPT

Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full addresses) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

Title page

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should also be suggested.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the experiments to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

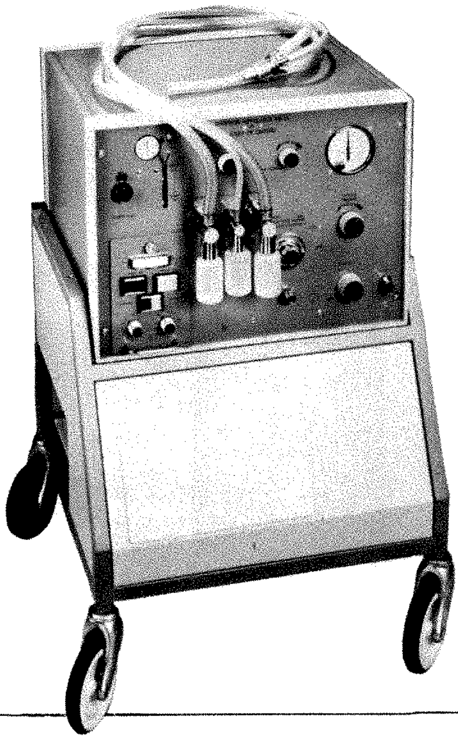
Description of experimental results, while concise, should permit repetition of the experiments by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of

EAST OF OXFORD

...is a name known throughout the world for advanced and reliable electro-mechanical anaesthetic apparatus.

East-Freeman Mk.2 Ventilator

Suitable for long or short-term use in ward or intensive care units – or in the operating theatre for controlled/assisted ventilation with anaesthetic gases.

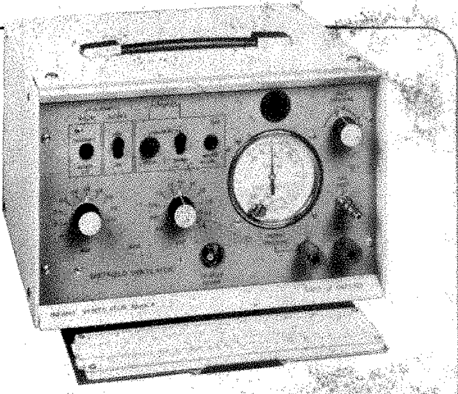


Hyperthermia Unit

This controlled water temperature unit will supply warm or cool water to a blanket within the 4°C to 40°C range. Readily portable, quiet, corrosion proof and reliable.

Humidifier Unit

East's blower-assisted humidifier unit provides a steady stream of warm, saturated air or oxygen for spontaneously breathing patients using tracheostomy boxes.



Sheffield Infant Ventilator Mk. 4

For anaesthesia or long-term ventilation of infants up to the age of three, the Mk. 4 unit is time-cycled, volume-controlled and pressure-limited with a wide range of respiratory rates.

The East-Radcliffe Mk. 5 Ventilator

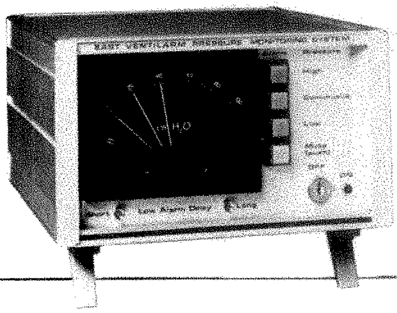
The latest model in a well-proven series – reliable and simple to operate. Autoclavable patient circuitry. Variable respiration rate. The unit may be used as a time-cycled pressure generator or as a volume-limited ventilator.

East-Radcliffe Respirator

A highly compact theatre trolley unit which can supply anaesthetic gases by hand or automatically. The unit will also function as a ward ventilator.

The East Ventilarm Pressure Monitor/Alarm System

The East Ventilarm provides maximum protection to a patient connected to a lung ventilator and is activated by any change in the pressure pattern.



H.G. EAST & COMPANY LTD.

Littlemore, Oxford. OX4 5JT. Tel: Oxford 779361

A subsidiary of British Syphon Industries Ltd.

digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

Discussion

The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially.

References

There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

In the case of books, the reference should be as follows: name of author and initials; year of publication in parentheses; title of book, underlined; number of edition; page number; town of origin, publisher; for example: Hill, D. W. (1971). *Physics Applied to Anaesthesia*, 2nd edn, p. 212. London: Butterworths.

The *British Journal of Anaesthesia* should be referred to as *Br. J. Anaesth.*

In the text up to three authors should be named before the use of "... et al.". If reference is made to several publications during a particular year, written by a larger group of authors who have alternated the order of authorship, as many names must be written as are necessary to distinguish between the publications, before use of "... et al." in conjunction with the year suffixes a, b, c.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase "(in press)" replacing volume and page number.

It is essential that authors verify the content and details of references which they list, as this responsibility cannot be accepted by either Editors or Publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ ◐
◑ ◒ ◉ ⊙ ⦶ ⊕ ⊖ ▩ ■ ▤ × +

The name of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It is emphasized that care taken in the original preparation of figures will obviate the time-consuming and expensive necessity of their revision.

When seconds count...

the MA-2 can be a lifesaver.

When a patient suddenly fails to breathe spontaneously during IMV or CPAP procedures, time can be critical. Simple warning systems may prove inadequate.
The MA-2 with its unique Fail-to-Cycle switchover mechanism not only warns the operator, but also automatically switches the MA-2 to a mandatory ventilation mode and controls the patient's ventilation at levels preselected by the operator until help arrives.
Those additional precious seconds of mandatory ventilation that only the MA-2 can provide may prove to be a lifesaver.
So buy the best... Buy Puritan-Bennett.

Puritan-Bennett International Corp.
Bognor Road, Chichester, Sussex PO19 2PH.
Telex: 86462. Cables: Puremade Chichester.
Serving Europe, the Middle East and Africa.

PURITAN-BENNETT CORPORATION

10th & Harrison, Berkeley, California 94710.
Serving Japan, Australia, the Philippines, India and the Pacific Orient
7280 N.W. 58th Street, Miami, Florida 33166.
Serving Central America, South America, Mexico and the Caribbean

General information

Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available:

1.	PART I	(capitals)
2.	RESULTS	(small capitals)
3.	Blood-gas analysis	(l.c. roman)
4.	*The action of drugs*	(italics, centre)
5.	*Lung function studies*	(italics, full out)
6.	*Volume.* Large volumes. . . .	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet "Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors" (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

CORRESPONDENCE

It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

PROOFS

These should be corrected and returned to the sub-editor *within 48 hours of receipt*. Overseas contributors should return their proofs by airmail.

REPRINTS

Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

Extension tubes?

Whatever your needs, when choosing the correct extension tube for a particular procedure, Vygon has the answer in the following range of kink-resistant tubes:

Lectro-Cath (code 1155) 1mm internal diameter male to female luer lock extension tube (tested to 4,000kPa).

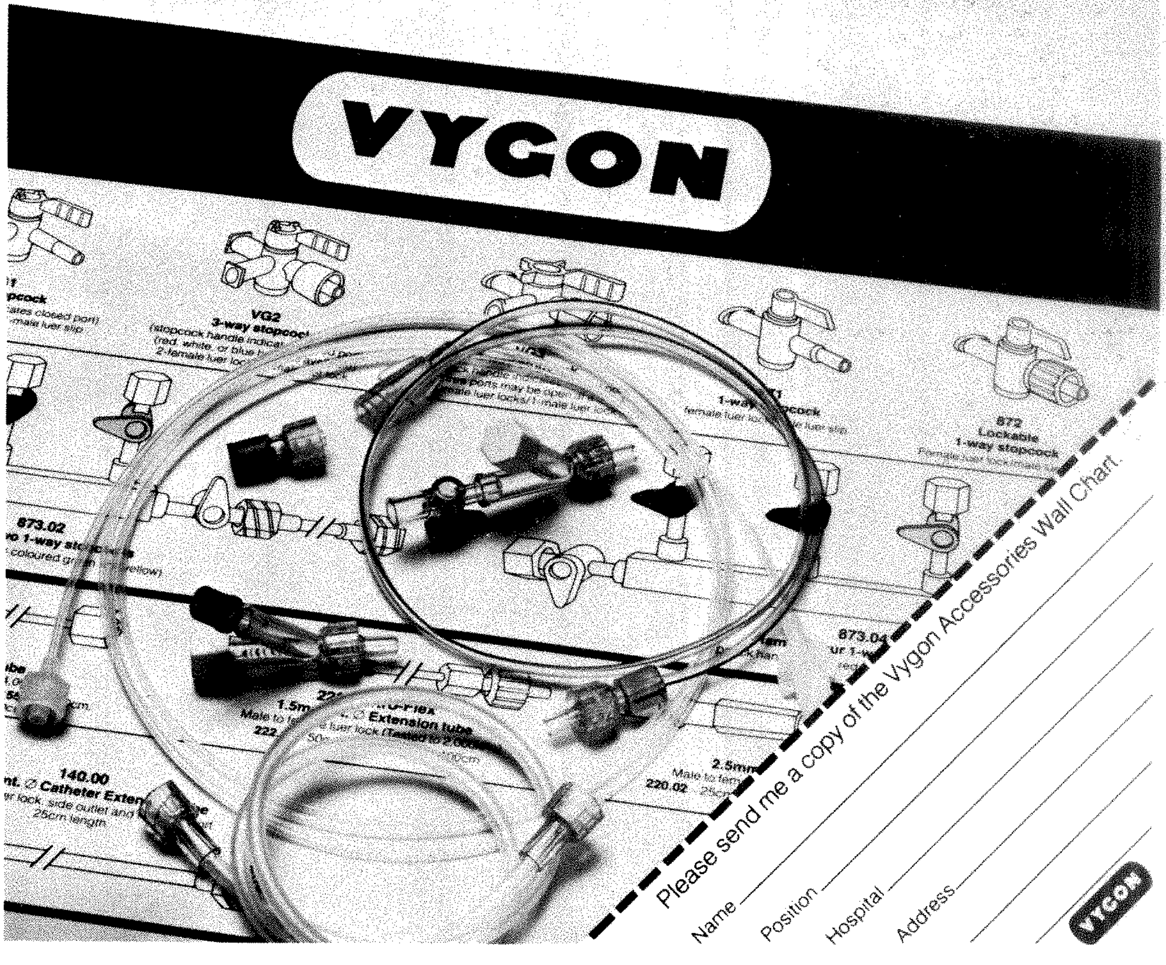
Lectro-Flex (code 222) 1.5mm internal diameter male to female luer lock extension tube. (tested to 2,000kPa).

Extension tube (code 220) 2.5mm internal diameter male to female luer lock (tested to 2,000kPa).

Extension tube (code 221) 2.5mm internal diameter male to male luer lock (tested to 2,000kPa).

Vygon extension tubes are part of a comprehensive range of quality, disposable accessories shown actual size on the new Vygon Accessories Wall Chart, which can be obtained by completing the coupon below and sending it to:

Vygon (UK) Limited,
Bridge Road, Cirencester,
Gloucestershire GL7 1PT
Telephone: Cirencester (0285) 67051



Please send me a copy of the Vygon Accessories Wall Chart.

Name

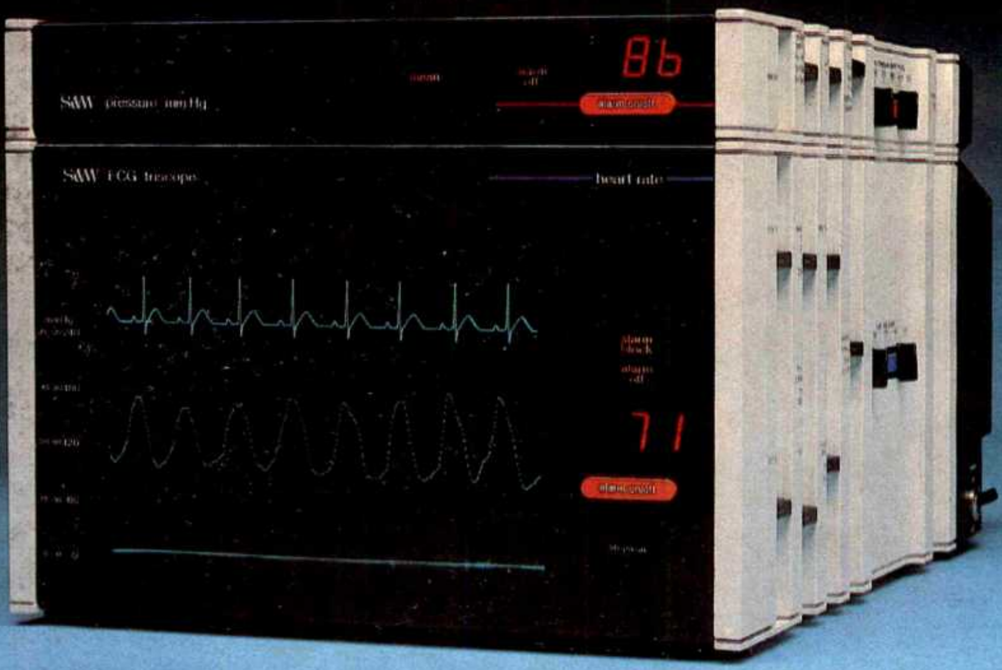
Position

Hospital

Address

VYGON

SYSTEM 8000

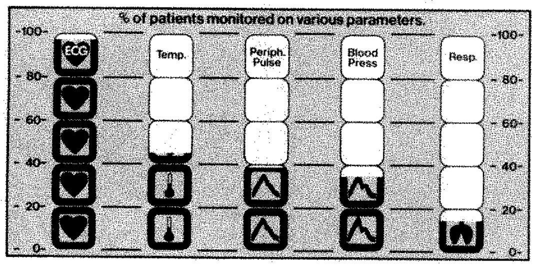


S&W

Simonsen & Weel Limited, Hatherley House, Hatherley Road, Sidcup, Kent DA 14 4BR. Tel: 01-300 1128

... a different approach to Patient Monitoring

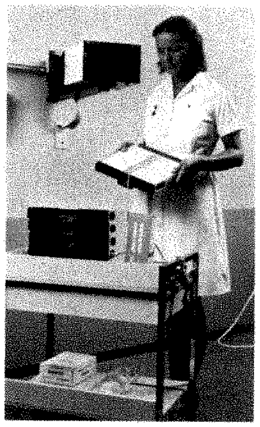
Electronic monitoring is now an accepted part of patient care. ECG is the most regularly monitored signal and the table below approximates to the percentage of patients monitored electronically for the more common parameters.



Today the cost of quality medical instrumentation does not allow there to be equipment in the Intensive or Coronary Care Unit which is not fully used or is unavailable for use on one patient because it is locked into a system on another. The S & W 8000 System allows total flexibility to match the instrumentation to the patient's need with the added advantages of:-

* Progressive expansion of the monitoring system as new modules for new parameters are developed
* Modules may be used with a low cost power supply as monitors in their own right; for example, pressure, temperature, respiration
* May be used in any department in the hospital; C.C.U., I.T.U., Operating Theatres, Neo-natal units
* Ease of servicing in event of unsatisfactory performances

The 8000 System is built to the high standards of safety and incorporates the recent advances in technology. Quality and reliability have been major design considerations. Let us show you how patient monitoring equipment should be made.



The 8000 System has been awarded the Industrial Design Award for 1979 and the Danish Plastics Industry Design prize 1979

You've worked hard for your money

-now let it work hard for you.

Like you, we at Lombard rely on our hard earned skills. Our experience over many years has made us an important name in British Banking and Finance to help people like you make their money grow by depositing with us.

We have a wide range of specially designed Deposit Account Schemes offering sound rates of interest which is paid without deduction of tax at source.

For further details of our deposit facilities and current interest rates without any obligation, simply post the coupon today.

Lombard North Central
Bankers

To:
LOMBARD NORTH CENTRAL LTD,
DEPT. U942,
17 BRUTON STREET,
LONDON W1A 3DH.
Tel: 491 7050

Name:
(BLOCK CAPITALS PLEASE)
Address:

A member of the National Westminster Bank Group whose capital and reserves exceed £1,300,000,000.

Anesthesiologists:

90 member multispecialty group adjacent to modern accredited 500 bed hospital seeks Board eligible or certified specialist to join associates; located in upper midwest university metropolitan area of 110,000; thirty-five minutes from superb clean lake region; associated with four year medical school; outstanding income; all specialties represented; will pay travel expenses for physician and spouse for interview.

Write: Box 002,
c/o Macmillan Journals, Ltd,
Advertising Department,
4 Little Essex Street,
London WC2R 3LF, England

CANADIAN ANAESTHETISTS' SOCIETY
JOURNAL

Editor
R. A. GORDON
Assistant Editor: GORDON WYANT
Editorial Board
MARCEL BOULANGER A. W. CONN DOUGLAS B. CRAIG
KENNETH M. LEIGHTON EMERSON MOFFITT R. A. MELOCHE BERNARD PAIEMENT

The Journal is issued bi-monthly for members of the Society and Subscribers. It contains original articles and reviews on clinical and basic science subjects related to Anaesthesia.

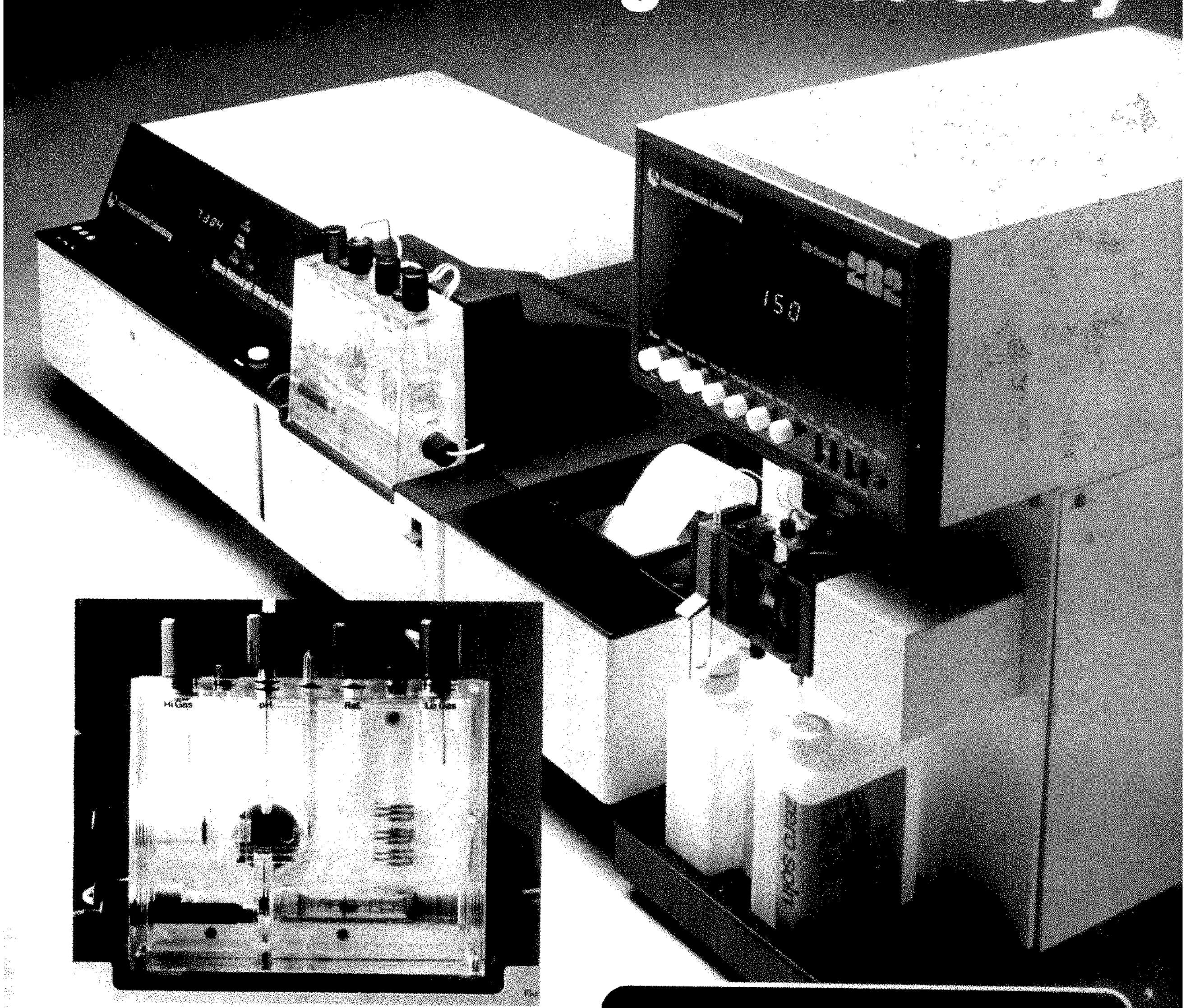
Annual Subscription $30.00 post paid

First Class Airmail $12.00 extra (optional).

The Secretary
Canadian Anaesthetists' Society
178 St. George Street, Toronto M5R 2M7, Ontario, Canada

Instrumentation Laboratory (UK) Limited announce the IL 617

Our total blood gas laboratory



A new first on the market from IL: **complete** blood gas analysis by actual direct measurement for both acid/base status and oxygen status.

Only the IL 617 can give the whole story of blood gas analysis: pH, PCO_2, PO_2, total Hb, oxygen saturation, % carboxyhaemoglobin and % methaemoglobin are analysed directly and are presented in printed format, together with base excess, total CO_2, standard bicarbonate, actual bicarbonate and O_2 content.

Standard advantages are:

- auto-calibration
- microsampling
- automatic flush
- total sample visibility
- data ready and data storage facility
- easy access to electrodes and cuvette

Each new blood gas analyser supplied by IL entitles the purchaser to:

- **Two free places on a blood gas seminar.**
- **Over £200 (worth) of our new QC material ContrIL™ with automatic entry into the European Proficiency Survey.**
- **Up to a £150 saving on the purchase of an IL237 Tonometer.**

When accuracy is vital.

Instrumentation Laboratory (UK) Limited
Kelvin Close, Birchwood Science Park,
Warrington, Cheshire, WA3 7PB
Tel: 0925 810141

June Publication

TOPICAL REVIEWS IN ANAESTHESIA, VOLUME 1

Edited by J. NORMAN, M.B., Ch.B., Ph.D., F.F.A.R.C.S., *Professor of Anaesthesia, University of Southampton Medical School, and* J. WHITWAM, M.B., Ch.B., Ph.D., F.F.A.R.C.S., *Reader in Anaesthesia, Royal Postgraduate Medical School, London.*

Contributors: Dr. C. Richards, Department of Physiology and Pharmacology, National Institute for Medical Research, London.
Dr. B. G. Covino, Department of Anaesthesiology, University of Massachusetts Medical Center, U.S.A.
Dr. F. J. M. Reynolds, Anaesthetic Unit, St. Thomas's Hospital Medical School, London.
Dr. J. M. Manners, Department of Anaesthetics, Southampton General Hospital

Contents: The Mechanisms of General Anaesthesia; The Mechanisms of Local Anaesthesia; Transfer of Drugs Across Membranes; Anaesthesia for Cardiac Surgery; Index.
This first volume in the new postgraduate series provides consultants, practitioners and research workers with a review of recent progress and current trends in anaesthesiology. Further volumes will be published at approximately two yearly intervals

216 x 138 mm, 288 pages, 64 illustrations **U.K. net price £13.50**
ISBN 0 7236 0539 4

JOHN WRIGHT
42-44 Triangle West, Bristol BS8 1EX

THE ROYAL LIVERPOOL AND ALDER HEY CHILDREN'S HOSPITALS

A SHORT COURSE IN PAEDIATRIC ANAESTHESIA

September 3–5, 1980

This course is for Senior Registrars and Consultants in anaesthesia and covers a broad spectrum of topics relating to paediatric anaesthesia.

Residential accommodation will be available in the University Halls of Residence at a cost of £26, including the course Dinner.

The entry fee will be £50 and the number of participants will be limited to 30. The last date for applications is July 1, 1980.

Further details and application forms from:
Dr G. Jackson Rees,
Consultant Anaesthetist,
Royal Liverpool Children's Hospital,
Myrtle Street,
Liverpool L7 7DG.

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 5 MAY 1980

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

EDITORIAL

NOT ALL THE WAY ON THE VANCOUVER STYLE

The Vancouver Style was proposed by 19 British, American and Canadian editors whose first meeting was at the city of Vancouver. Their aim was to provide uniform guidance to those preparing manuscripts for submission to bio-medical journals. The need for uniformity is easily recognized by both authors and editors, for considerable difficulties may arise if a paper is prepared in a format which is different from that adopted by a journal; indeed many journals refuse to accept such manuscripts. The problem of disparity of style is highlighted in the case of a manuscript which has been rejected by one journal and is being prepared for submission to another editor whose needs are substantially different.

The details of the Vancouver proposals have been published widely, for example in the *British Medical Journal* (1979) **1**, 532–535. Guidance is given on the layout of manuscripts, including instructions to typists, on the appropriate content of the several parts of the paper, the use of abbreviations, and on the preparation of tables and illustrations. All of this is broadly in accord with the style at present adopted by *British Journal of Anaesthesia* and described in detail in our *Extended Guide to Contributors* published in May 1978 (**50**, 531–538).

There is, however, one important respect in which *British Journal of Anaesthesia* does not conform to the Vancouver proposals—the method of citing and listing of references. The Vancouver meeting called for a standard numbered system of referencing in which each reference receives a superscript number according to the order of its appearance in the text; the references are listed in numerical order at the end of the manuscript, each entry on the list comprising the names of the authors, title of the paper, the name of the journal in full, the year of publication, volume number and first and last pages within the volume. *British Journal of Anaesthesia* prefers the so-called Harvard system in which the names of up to three authors are given within the text together with the year of publication; in the reference list the entries appear in alphabetical order according to the surname of the first author. Further details of our system and the Vancouver system, particularly with regard to the citing of material contained in textbooks and pamphlets, can be found in the publications referred to above.

After careful consideration the Editorial Board of *British Journal of Anaesthesia* felt, as did the Boards of several other journals, that the Harvard system should be maintained because it seems to offer important advantages over the numbered system. The citing of names within the text may aid the reader in assessing the likely quality of the material referred to. Similarly, the editor and reader–assessor are assisted in their task and the occasional occurrence of an inappropriately cited reference is spotted more easily. The numbered system carries the risk that an error in transcription, "17" entered wrongly as "7" for example, will result in the reference being irretrievably lost within the presentation.

The advantages of the numbered system are that space is saved within the text and that re-drafting of a manuscript for a second editor is facilitated by standardization. We consider, however, that the primary objective of communication is served better by the Harvard system. Although we would wish to afford secretaries and typists every reasonable consideration it is a fact, for the specialist journals at least, that submission to a second editor often necessitates revision of the text so that the occasions on which a rejected manuscript is simply re-addressed should be rare.

Our plan to continue with the Harvard system in this Journal is influenced by two additional factors. Publications which adopted the Vancouver proposals *in toto* did so formally on January 1, 1980, a date referred to optimistically as Standard Style Day. In the period that has elapsed since then we have not become aware of any difficulties for us or for any other journals sharing our views as a result of the disparity. We were also influenced, in a more general way, by the problem which followed the adoption of the S.I. system of units in the 1970s. Although there can be no question of departing from that policy now, it has to be recognized that the changes which occurred at that time, for example with regard to the use of the kilopascal, have not been widely accepted in day-to-day clinical parlance.

If we had decided to adopt the Vancouver system of references there are many reasons why such a change would be irrevocable. Our decision to continue with the Harvard system is not irrevocable and we would welcome constructive comments by any of our readers or contributors who feel strongly on the matter.

A. A. Spence

Br. J. Anaesth. (1980), **52**, 471

ENFLURANE HAS NO EFFECT ON HAEMOPOIESIS IN MICE

J. M. BADEN, B. EGBERT AND S. A. RICE

SUMMARY

Male and female Swiss/ICR mice were exposed to 0.3% enflurane in air, 4 h per day, 5 days per week for 52 weeks. A control group was exposed to air alone. After 52 weeks, all animals were sacrificed and peripheral blood and bone marrow samples were examined for alterations in haemopoiesis. In general, there was no difference between treated and control groups.

Since Lassen and colleagues (1956) first described severe bone marrow depression after prolonged nitrous oxide anaesthesia in patients with tetanus, several investigators have studied the haemopoietic effects of inhalation anaesthetics in animals. Most have studied anaesthetic administration for up to 8 days, simulating patient exposure (Eastwood, 1963; Green, 1964; Bruce and Koepke, 1966; Aldrete and Virtue, 1968). More recently, Cleaton-Jones and colleagues (1977) described haemopoietic effects in rats following intermittent exposure to nitrous oxide for 6 months. They designed their study as a model of occupational exposure to waste anaesthetic gases.

We have examined the haemopoietic effects of long-term exposure to enflurane (2-chloro-1,1,2-trifluoroethyl difluoromethyl ether), in mice.

METHODS

Forty-eight Swiss/ICR weanling mice were kept in quarantine for 5 days, and randomly divided into two groups each containing 12 males and 12 females. Throughout the experiment, they were accommodated four to a cage and were bedded on ground corn cob in polypropylene plastic cages with zinc-coated lids. They were fed small animal chow and allowed to drink tap water *ad libitum* except during anaesthetic exposure, when food and water were removed. There was a fixed diurnal cycle of 12 h light and 12 h darkness, with exposure during the light phase.

Group 1 (control) were exposed to medical grade compressed air and group 2 to 0.3% (3000 p.p.m. v/v) enflurance vapour in air. Enflurane (Ohio Medical Products, Madison, Wisconsin) was the commercially available product. The duration of exposure was 4 h per day, 5 days per week for 52 weeks. This regimen was determined in preliminary studies and provided the maximum tolerated dose of enflurane which did not cause greater than 10% loss of body weight or early death.

Exposures were performed in two air-tight stainless steel and Plexiglass chambers each of 1500 litre capacity; one chamber was used exclusively for enflurane. For exposure, the cages were placed randomly in the chambers. Enflurane in medical grade compressed air, from a Copper Kettle vaporizer, was conducted through rubber tubing to the chamber. There was an electric fan at each end of the chamber. At the beginning and middle of the experiment, concentrations were checked at several sites in the chamber and within individual cages to confirm that there was even distribution. Gas was sampled with a gas-tight syringe through stop-cocks at each end of the chamber. Enflurane concentration was determined using a Varian 1440 gas chromatograph and checked every few minutes until it reached the desired concentration, usually by the 10th min. After equilibrium this analysis was repeated every 15 min. Throughout exposure, the enflurane concentration was maintained within a 5% tolerance limit, and temperature and humidity at 25 ± 2 °C and 50 ± 10%, respectively. Carbon dioxide concentration was always less than 0.3%. At the end of exposure, the enflurane chamber was exhausted to a fume hood for 15 min before the door was opened and animals removed; at no time were laboratory personnel exposed to

---

JEFFREY M. BADEN, M.B., B.S., F.F.A.R.C.S., M.R.C.P.(UK); BARBARA EGBERT, M.D.; SUSAN A. RICE, PH.D.; Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305, and Veterans Administration Medical Centre, Palo Alto, California 94304, U.S.A.

Correspondence to J. B., Anesthesiology Service (112A), Veterans Administration Hospital, 3801 Miranda Avenue, Palo Alto, California 94304, U.S.A.

0007-0912/80/050471-04 $01.00

© Macmillan Journals Ltd 1980

COLLEGE OF ME
LIBRARY

enflurane concentrations exceeding 0.5 p.p.m. The control chamber was exhausted similarly.

Mice were observed at least once daily and any abnormal findings were noted; they were weighed at monthly intervals.

On the day of sacrifice, each animal was weighed then killed by exposure to carbon dioxide. The abdominal and chest cavities were opened and blood collected by cardiac puncture into 10% EDTA 0.2 ml. Total volume was recorded in order to calculate the dilution factor as a result of EDTA. Bone marrow was obtained from the femur using a sharp needle and smears were prepared. The liver, spleen, several thoraco-lumbar vertebrae with bone marrow *in situ* and several mesenteric or mediastinal lymph nodes were fixed in 10% buffered formalin for possible histological examination. Bone marrow and blood smears were air dried and treated with Wright-Giemsa stain. Bone marrow smears were viewed and blood was examined, either using a Coulter Counter S or by direct observation of blood slides, to determine white blood cell, red blood cell and platelet counts, haemoglobin concentration, packed cell volume, mean cell volume, mean cell haemoglobin content, mean cell haemoglobin concentration, differential white cell count and reticulocyte count.

RESULTS

Throughout the experiment, male and female animals exposed to enflurane weighed about 5% less than the controls (fig. 1). There were no other enflurane-related effects on physical appearance or behaviour. Several males developed skin ulcers and abscesses as a result of fighting and two animals had rectal prolapses. Other minor lesions such as eye and ear infections and alopecia were observed occasionally. These lesions occurred with equal frequency in the two groups.

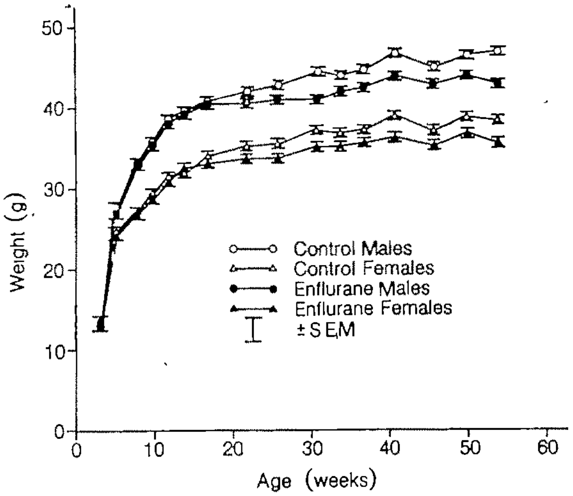


FIG. 1. Mean body weights (±SEM) for each group from start of exposure at weaning until end of exposure at sacrifice. Male and female enflurane-treated animals showed a weight decrease of about 5% throughout the exposure period.

There were no consistent differences in haematological values between the groups for either males or females (tables I and II). The only statistically significant differences occurred with enflurane-treated male animals which had a greater average lymphocyte count (60% *v.* 51%, $P<0.05$) and a smaller average reticulocyte count (1.0% *v.* 1.9%, $P<0.01$) than control males (table II). However, all values were within the normal range for mice (Payne et al., 1976). In view of the other normal haematological values and normal bone marrow findings, these statistical differences were not considered to be biologically significant; one enflurane-exposed male had 23% monocytes and one control female 5.4% reticulocytes. Although above group averages for these indices, they were isolated findings in otherwise healthy animals and were not considered abnormal.

TABLE I. *Haematological values (mean ± SEM). WBC = white blood cells; RBC = red blood cells; Hb = haemoglobin; PCV = packed cell volume; MCV = mean cell volume, MCH = mean cell haemoglobin content; MCHC = mean cell haemoglobin concentration*

Groups (*n*)	WBC (cell litre^{-1}) ($\times 10^9$)	RBC (cell litre^{-1}) ($\times 10^{12}$)	Platelet (per litre) ($\times 10^{12}$)	Hb (g dl^{-1})	PCV (%)	MCV (μm^3)	MCH (pg)	MCHC (μg dl^{-1})
Male								
Control (12)	9.0 ± 0.7	7.6 ± 0.2	1.4 ± 0.2	13.7 ± 0.3	33.0 ± 0.6	44.2 ± 0.5	18.0 ± 0.1	41.0 ± 0.4
Enflurane (12)	10.9 ± 1.1	7.9 ± 0.3	1.7 ± 0.2	14.2 ± 0.6	35.3 ± 1.6	43.8 ± 0.6	17.2 ± 0.8	41.0 ± 0.4
Female								
Control (12)	9.5 ± 0.8	6.8 ± 0.27	1.1 ± 0.1	12.7 ± 0.5	31.5 ± 1.3	45.6 ± 0.5	18.6 ± 0.2	40.9 ± 0.3
Enflurane (12)	8.7 ± 0.7	7.2 ± 0.3	1.2 ± 0.1	13.1 ± 0.5	33.0 ± 1.4	45.1 ± 0.4	18.4 ± 0.2	40.7 ± 0.3

TABLE II. *Values for differential white cell count and reticulocyte count* (*mean* ± *SEM*). **Significantly greater than control* ($P < 0.05$); ***Significantly less than control* ($P < 0.01$)

Group (*n*)	Neutrophils (%)	Lymphocytes (%)	Eosinophils (%)	Basophils (%)	Monocytes (%)	Reticulocyte count (%)
Male						
Control (12)	40.1 ± 3.0	50.9 ± 2.6	3.2 ± 0.6	0.2 ± 0.1	5.6 ± 1.1	1.9 ± 0.2
Enflurane (12)	32.6 ± 3.4	60.0 ± 3.2*	2.9 ± 0.6	0.2 ± 0.1	4.3 ± 1.5	1.0 ± 0.2**
Female						
Control (12)	28.8 ± 3.1	64.8 ± 5.7	2.4 ± 0.6	0.2 ± 0.1	3.8 ± 0.7	1.2 ± 0.4
Enflurane (12)	26.5 ± 2.5	66.9 ± 3.0	2.0 ± 0.6	0.3 ± 0.2	4.3 ± 0.7	1.2 ± 0.3

Bone marrow smears from all animals showed normal ratios of red cell, white cell and platelet precursors. Maturation in all series appeared normal and there was no evidence of haemopoietic malignancy.

DISCUSSION

In this study, chronic intermittent exposure to enflurane had no effect on haemopoiesis in male or female Swiss/ICR mice. Enflurane 0.3% was administered 4 h per day, 5 days per week—a maximum tolerated dose for this mouse strain. Greater doses would have led to greater than 10% body weight loss compared with unexposed controls; such profound nutritional deficiency would have increased the difficulty in the interpretation of results. On the other hand, smaller doses would have decreased the sensitivity of the study. The enflurane concentration, 0.3% (3000 p.p.m.), exceeded the concentrations expected even in unscavenged operating rooms. Thus, the negative results obtained at this large concentration make it unlikely that smaller concentrations, such as those present in the operating suite, would produce an effect on haemopoiesis. Exposures were carried out for 52 weeks, which is about half the life-span of a mouse.

To assess the possible hazard to operating room personnel, several investigators have examined the haemopoietic effects of chronic intermittent exposure to inhalation anaesthetics in animals. Cleaton-Jones and colleagues (1977) exposed Wistar strain albino rats to 1% nitrous oxide for periods ranging from 1 week to 6 months. Apart from transient polycythaemia which occurred during the first week of exposure, they detected no change in haemopoiesis. The reports from two long-term carcinogenicity studies of inhalation anaesthetics have included haematological data. In a study with Fischer 344 rats, Coate, Kapp and Lewis (1979) looked at effects on the reticulo-endothelial system of 24 months' exposure to small concentrations of a nitrous oxide in halothane combination. Concentrations used were halothane 1 p.p.m. and nitrous oxide 50 p.p.m., and halothane 10 p.p.m. and nitrous oxide 500 p.p.m. Haematological evaluation showed large variations in percentages of monocytes among groups in both males and females, but no consistent effects related to treatment. Other haematological variables, including bone marrow analyses, were within normal limits. In a study by Baden and colleagues (1979), Swiss/ICR mice were exposed to 0.05% (500 p.p.m.) halothane *in utero* for 10 days and postnatally for 18 months. No haematological effects related to treatment were observed.

Thus, to date, there is no experimental evidence that chronic intermittent exposure to subanaesthetic concentrations of inhalation anaesthetics has adverse effects on haemopoiesis.

ACKNOWLEDGEMENTS

The authors wish to thank Ohio Medical Products, Madison, Wisconsin, for kindly supplying enflurane and Mr Espano-Barros for his excellent technical assistance. The study was supported by the VA Medical Centre, Palo Alto, California.

REFERENCES

Aldrete, J. A., and Virtue, R. M. (1968). Effects of prolonged inhalation of anesthetic and other gases on blood and marrow of rats; in *Toxicology of Anesthetics* (ed. B. R. Fink), p. 105. Baltimore: Williams and Wilkins.

Baden, J. M., Mazze, R. I., Wharton, R. S., Rice, S. A., and Kosek, J. C. (1979). Carcinogenicity of halothane in Swiss/ICR mice. *Anesthesiology*, **51**, 20.

Bruce, D. L., and Koepke, J. A. (1966). Changes in granulopoiesis in the rat associated with prolonged halothane anesthesia. *Anesthesiology*, **27**, 811.

Cleaton-Jones, P., Austin, J. C., Banks, D., Vieira, E., and Kagan, E. (1977). Effect of intermittent exposure to a low concentration of nitrous oxide on haemopoiesis in rats. *Br. J. Anaesth.*, **49**, 223.

Coate, W. B., Kapp, R. W., and Lewis, T. R. (1979). Chronic exposure to low concentrations of halothane–nitrous oxide; reproductive and cytogenetic effects in the rat. *Anesthesiology*, **50**, 310.

Green, C. D. (1964). The toxicity of nitrous oxide. *Clin. Anesth.*, **1**, 38.

Eastwood, D. W. (1963). Effects of nitrous oxide inhalation on hemopoiesis in rats. *Anesthesiology*, **24**, 341.

Lassen, H. C. A., Henriksen, E., Neukirch, F., and Kristensen, H. S. (1956). Treatment of tetanus: severe bone marrow depression after prolonged nitrous oxide anaesthesia. *Lancet*, **1**, 527.

Payne, B. J., Lewis, H. B., Murchison, T. E., and Hart, E. A. (1976). Hematology of laboratory animals; in *CRC Handbook* (eds E. C. Melby jr and N. H. Altman), p. 449. Cleveland, Ohio: CRC Press, Inc.

L'ENFLURANE N'A AUCUN EFFET SUR L'HEMOPOIESE DES SOURIS

RESUME

Des souris suisses/ICR, mâles et femelles, ont été exposées pendant 4 h par jour, 5 jours par semaine et ce pendant 52 semaines, à 0,3% d'enflurane dans l'air. Un groupe témoin n'a été exposé qu'à l'air seul. Après 52 semaines, tous les animaux ont été sacrifiés et on a examiné des échantillons de sang périphérique et de moelle des os pour déceler les modifications résultant de l'hémopoièse. Il n'y a eu, dans l'ensemble, aucune différence entre le groupe traité et le groupe témoin.

ENFLURAN HAT KEIN WIRKUNG AUF HÄMATOPOESE IN MÄUSEN

ZUSAMMENFASSUNG

Mannliche und weibliche Schweizer/ICR-Mause wurden 4 Stunden taglich, 5 Tage pro Woche auf 52 Wochen einer Dosis von 0,3% Enfluran in Luft ausgesetzt. Eine Kontrollgruppe wurde nur der Luft ausgestzt. Nach 52 Wochen wurden periphere Blut- und Markproben aller Tiere auf Änderungen im Bezug auf Hamatopoese untersucht. Es zeigten sich im allgemeinen keine Unterschiede zwischen behandelter und Kontrollgruppe.

FLURANO NO TIENE EFECTO EN LA HEMOPOIESIS DE LOS RATONES

SUMARIO

Se expuso a ratones suizos/ICR machos y hembras al enflurano al 0,3% en el aire, 4 h por día, 5 días por semana durante 52 semanas. Se expuso a un grupo de control al aire únicamente. Después de 52 semanas, se sacrificó a todos los animales y se examinó muestras de sangre periférica y de médula ósea en búsqueda de las alteraciones de la hemopoiesis. En general, no había diferencia alguna entre los grupos de control y los grupos tratados.

Br. J. Anaesth. (1980), **52**, 475

CARDIORESPIRATORY EFFECTS OF HIGH FREQUENCY INTERMITTENT POSITIVE PRESSURE VENTILATION IN THE DOG

M. K. CHAKRABARTI and M. K. SYKES

SUMMARY

The cardiorespiratory effects of increasing respiratory frequency were investigated in two groups of dogs ventilated mechanically with a system which minimized apparatus and anatomical deadspace. In one group minute volume was constant whilst frequency was increased; in the second group minute volume was increased to maintain normal Pa_{CO_2}. The reduction in tidal volume with increasing frequency was accompanied by a reduction in physiological deadspace. However, the reduction in deadspace was proportionally less than the decrease in tidal volume, so that the deadspace/tidal volume ratio increased. The peak airway pressures were minimal at a frequency of 45 b.p.m. At frequencies of 60 b.p.m. and more, the lung failed to empty so that peak airway pressures were increased and cardiac output decreased.

During mechanical ventilation the tidal volume is determined by the change in alveolar pressure and the total thoracic compliance. When lung compliance is reduced alveolar ventilation can only be maintained by increasing the transpulmonary pressure difference or by increasing the frequency of ventilation. Since an increase in transpulmonary pressure increases pulmonary vascular resistance and may also result in pneumothorax or pneumomediastinum, it is generally accepted that it is safer to increase frequency when there is a marked reduction in lung compliance. However, the presence of the apparatus and anatomical deadspace limits the increase in frequency and reduction in tidal volume which can be tolerated. Furthermore, at high frequencies, variations in regional time constants may lead to impaired gas distribution and there may also be insufficient time for the lung to empty. Since previous studies on the physiological effects of increasing the frequency of mechanical ventilation have been confined to a limited range of frequencies, the present experiments were designed to determine the practicable upper limits of frequency which could be used when the apparatus and anatomical deadspaces were reduced to a minimum.

METHODS

Experimental methods. The experiments were performed on nine supine dogs of different breed weighing between 15 and 28 kg. Anaesthesia was induced with thiopentone 20–30 mg kg^{-1} and a special cuffed tube was inserted into the trachea. The lung ventilator was set at a rate of 15 b.p.m. and the tidal volume adjusted to produce normocapnia. Anaesthesia was maintained with pentobarbitone, a total dose of 15–20 mg kg^{-1} being given over the study period of 5–6 h.

Cannulae were inserted into the right femoral artery and vein for cardiac output measurement by the dye dilution method, into the left femoral artery for pressure recording and blood sampling and into the left femoral vein for pressure recording. Oesophageal pressure was measured by inserting an oesophageal balloon into the middle third of the oesophagus and then adjusting its position to produce the maximum sub-atmospheric pressure. All pressures were recorded with Consolidated Electrodynamics strain gauges and a Devices M19 heated-stylus recorder. The transducers were repeatedly calibrated against saline columns.

Ventilation circuit. The ventilator was designed to deliver a constant inspiratory flow rate despite changes in impedance (fig. 1). Power was derived from a cylinder of compressed air, the driving pressure being maintained at 70 kPa (10 lbf in^{-2}) by a regulator (MSG30.0G (B.O.C.)). The inspiratory flow rate was controlled by a needle valve and flowmeter and the duration of inspiration and expiration was determined by conventional poppet valves operated by two cams on a common camshaft. The design of the cams was such that the inspiratory : expiratory time ratio was 1 : 2, both valves being closed for a short period (15°) at the end of each inspiratory

---

M. K. CHAKRABARTI, M.PHIL., B.SC.; M. K. SYKES, M.B., B.CHIR, F.F.A.R.C.S., F.F.A.R.A.C.S.(HON); Department of Anaesthetics, Royal Postgraduate Medical School, Hammersmith Hospital, DuCane Road, London W12 0HS.

0007–0912/80/050475–08 $01.00

© Macmillan Journals Ltd 1980

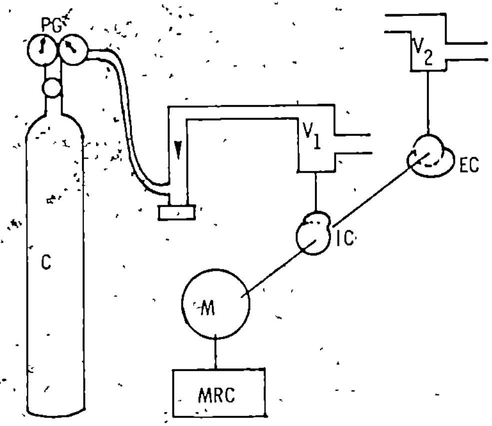


FIG. 1. The high frequency ventilator circuit. M = motor; MRC = motor r.p.m. controller; IC = inspiratory cam; V_1 = inspiratory valve; EC = expiratory cam; V_2 = expiratory valve; PG = reducing valve with two stage pressure gauge; G = gas cylinder.

and expiratory phase so that the end-inspiratory and end-expiratory pressures reflected the alveolar pressure. The frequency of ventilation was determined by a thyristor-controlled electric motor driving the camshaft. Since one complete rotation of the camshaft represented one breathing cycle, a tachometer could be used to measure respiratory frequency.

The ventilator was connected directly to concentric inspiratory and expiratory tubes (fig. 2). The expiratory tube was a standard, cuffed 11-mm i.d. plastic endotracheal tube 30 cm in length, whilst the inspiratory tube was a rigid plastic tube of 2 mm i.d. which extended almost to the tip of the outer tube. The airway pressure was sensed from a side-arm between the endotracheal tube and expiratory valve.

The ventilator and patient circuit was tested against a standard lung model with a compliance of 50 ml cm H_2O^{-1} and airway resistance of 5 cm H_2O litre^{-1} s (Loh, Sykes and Chakrabarti, 1978). The flow, pressure and volume waveforms are shown in figure 3. The valves were checked extensively for leaks but none occurred. The pressure difference across the whole expiratory ventilation circuit was found to be 0.25 kPa (2.5 cm H_2O) at a flow of 0.5 litre s^{-1}.

Programme of study

Group 1. The frequency of ventilation was increased in steps from 15 to 30, 60, 100, 170, 300 and 450 b.p.m., maintaining the minute ventilation constant.

Group 2. The frequency of ventilation was increased in similar steps but the minute ventilation was increased to keep Pa_{CO_2} constant.

The lungs of five dogs were ventilated according to the programme for group 1. In the first two it was found that, when the frequency was increased to 100 b.p.m., the carbon dioxide tension could not be kept within the normal range. The ventilating frequency was quickly increased in steps to 170, 300 and 450 b.p.m. but $P\text{CO}_2$ increased and the dogs died. In the remaining three dogs the maximum ventilation frequency was restricted to 100 b.p.m. Seven dogs were treated according to the programme for group 2. However, the frequencies of 300 and 450 b.p.m.,

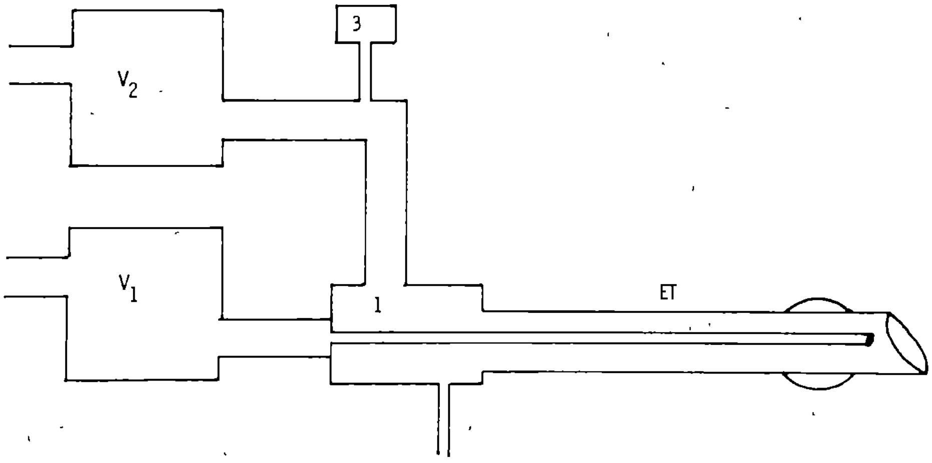


FIG. 2. Patient tubing with insufflation catheter. ET = endotracheal tube; 1 = insufflation catheter; 2 = airway pressure monitor; 3 = pressure relief valve.

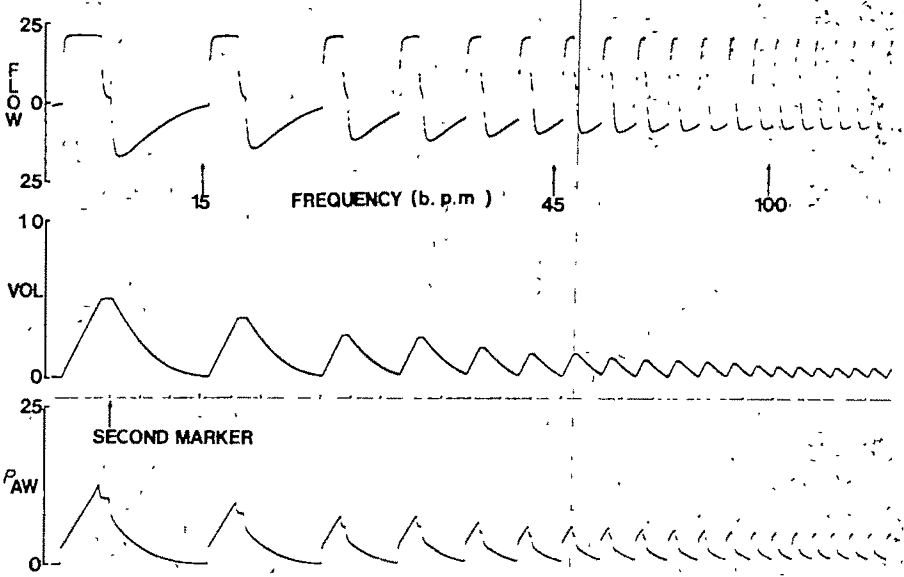


FIG. 3. Flow (litre min^{-1}), volume (litre) and airway pressure (cm H_2O) traces showing the inspiratory flow pattern and I : E ratio of the high frequency ventilator when ventilating a standard lung model at increasing frequencies.

and an additional frequency of 45 b.p.m., were used only in the last four dogs of this group.

Measurements. The expired gas was collected in a wet spirometer which had been modified to provide an electrical output for recording. The calibration of the spirometer was checked repeatedly by injecting a known volume from a large syringe. Duplicate blood samples were analysed for Po_2, Pco_2 and pH on two different electrode systems (Radiometer EPHM71 and ABL 1). All blood-gas tensions were expressed at body temperature using the factors of Kelman and Nunn (1966). Duplicate cardiac output measurements were made with the dye dilution technique using cardiogreen dye and a Gilford cuvette and withdrawal system. The curves were analysed by the method of Simons and White (1976). The mixed expired carbon dioxide was analysed with an infra-red carbon dioxide analyser (URAS 4, Hartmann–Braun) calibrated with previously analysed carbon dioxide–air mixtures. The physiological deadspace was calculated from Pa_{CO_2} and the mixed expired carbon dioxide tension ($P\bar{E}_{CO_2}$) using Enghoff's modification of the Bohr equation.

RESULTS

Table I summarizes the results of the experiments in group I in which the minute volume was held constant and the frequency was increased in steps from 15 to 30, 60 and 100 b.p.m. A two-way analysis of variance did not show any significant changes in minute volume ($\dot{V}E$) or cardiac output ($\dot{Q}$). Tidal volume (VT) decreased as the frequency increased, but the physiological deadspace/tidal volume ratio (VD/VT) increased with the increase in frequency since the physiological deadspace (VD) did not decrease in proportion to the decrease in VT. As a result the alveolar ventilation ($\dot{V}A$) decreased and Pa_{CO_2} increased. The peak airway pressure ($P_{AW}{}^{(peak)}$) decreased as frequency was increased and at 100 b.p.m. it was approximately 50% of the value at 15 b.p.m. However, although mean airway pressures decreased up to 60 b.p.m. they increased thereafter because of the development of an end-expiratory positive pressure ($P_{AW}{}^{(EEP)}$).

The results of the experiments in seven dogs in group 2 are shown in table II. The data were subjected to a two-way analysis of variance followed by paired t tests where appropriate. There were no significant changes in Pa_{O_2}, Pa_{CO_2} and $\dot{V}A$. To maintain Pa_{CO_2} constant, $\dot{V}E$ had to be increased when the frequency was increased. However, the increase was not in proportion to the increase in frequency or decrease in tidal volume and there was no significant difference in $\dot{V}E$ between the frequencies of 15 and 30 b.p.m. When the frequency was increased from 15 to 30 b.p.m. the physiological deadspace

TABLE I. *Group 1. Mean values ± SD in five dogs in which minute volume was maintained constant as frequency was increased.* $P_{AW}^{(peak)}$ *= peak airway pressure;* $P_{AW}^{(mean)}$ *= mean airway pressure;* $P_{AW}^{(EEP)}$ *= end-expiratory airway pressure*

	Frequency (b.p.m.)			
	15	30	60	100
$\dot{V}_E$ (litre min^{-1})	7.38 ± 1.9	7.38 ± 1.9	7.38 ± 1.8	7.2 ± 2.0
V_T (ml)	488.6 ± 120.1	253.4 ± 70.3	121.7 ± 32.9	71.7 ± 20.9
V_D (ml)	217.1 ± 38.5	135.2 ± 44.6	72.4 ± 21.7	55.4 ± 13.0
V_D/V_T (%)	44.4 ± 6.0	53.4 ± 3.8	59.5 ± 6.9	77.2 ± 5.6
$\dot{V}_A$ (litre min^{-1})	4.1 ± 1.3	3.6 ± 0.8	3.0 ± 0.8	1.6 ± 0.8
Pa_{O_2} (kPa)	13.1 ± 0.65	12.2 ± 0.31	10.7 ± 1.57	7.8 ± 2.3
Pa_{CO_2} (kPa)	4.1 ± 0.51	4.5 ± 0.37	5.5 ± 0.79	6.9 ± 1.29
$\dot{Q}$ (litre min^{-1})	2.6 ± 0.8	2.5 ± 0.75	2.9 ± 1.0	2.5 ± 0.8
$P_{AW}^{(peak)}$ (cm H_2O)	8.6 ± 1.1	5.9 ± 0.8	4.5 ± 1.3	4.0 ± 0.8
$P_{AW}^{(mean)}$ (cm H_2O)	3.4 ± 0.2	2.5 ± 0.6	2.2 ± 0.7	2.4 ± 0.7
$P_{AW}^{(EEP)}$ (cm H_2O)	0	0	0.6 ± 13	1.3 ± 0.4

TABLE II. *Group 2. Mean values ± SD in seven dogs in which arterial carbon dioxide tension was maintained constant. The letters in the table indicate the statistical comparisons in which* $P < 0.05$. P_{oes} *= end-expiratory oesophageal pressure;* $P_{oes}^{e\text{-}insp.}$ *= end-inspiratory oesophageal pressure*

	Frequency (b.p.m.)				
	A 15	B 30	C 60	D 100	E 170
$\dot{V}_E$ (litre min^{-1})	5.3 ± 1.6	5.8 ± 2.0 CDE	8.4 ± 2.8 ABDE	12.5 ± 4.6 ABCE	17.4 ± 6.7 ABCD
V_T (ml)	341.5 ± 96.0	195.2 ± 68.8 ACDE	141.3 ± 48.1 ABE	124.5 ± 45.7 AB	104.6 ± 39.0 ABC
V_D (ml)	154.6 ± 62.5	99.2 ± 47.3 A	93.3 ± 46.0 A	93.8 ± 48.3 A	88.5 ± 39.2 A
V_D/V_T (%)	45.3 ± 9.5	50.8 ± 11.5 CDE	66.0 ± 13.8 ABDE	75.4 ± 15.1 ABCE	84.6 ± 9.9 ABCD
$\dot{V}_A$ (litre min^{-1})	2.8 ± 0.7	2.9 ± 0.8	2.9 ± 0.6	3.1 ± 0.7	2.7 ± 0.3
Pa_{O_2} (kPa)	11.7 ± 1.05	11.5 ± 1.0	11.7 ± 0.68	12.1 ± 0.72	11.7 ± 0.91
Pa_{CO_2} (kPa)	4.6 ± 0.21	4.7 ± 0.29	4.6 ± 0.36	4.7 ± 0.25	4.7 ± 0.31
$\dot{Q}$ (litre min^{-1})	2.5 ± 0.7	2.7 ± 0.9 CDE	2.1 ± 0.7 BDE	1.9 ± 0.4 ABE	1.6 ± 0.4 ABC
$P_{AW}^{(peak)}$ (cm H_2O)	9.2 ± 1.4	6.7 ± 1.4 ADE	6.5 ± 2.3 ADE	8.4 ± 2.6 BCE	10.5 ± 3.7 BCD
$P_{AW}^{(mean)}$ (cm H_2O)	3.1 ± 0.7	2.6 ± 0.8 DE	3.6 ± 1.5 E	4.8 ± 2.8 E	7.1 ± 4.2 ABCD
$P_{AW}^{(EEP)}$ (cm H_2O)	0	0	0.8 ± 0.6	2.2 ± 2.0 ABC	4.1 ± 2.8 ABC
P_{oes} (cm H_2O)	−4.9 ± 0.7	−4.9 ± 0.9 E	−4.4 ± 1.4 E	−4.1 ± 1.2 E	−2.8 ± 1.2 ABCD
$P_{oes}^{e\text{-}insp.}$ (cm H_2O)	−1.7 ± 1.0	−2.2 ± 0.9	−2.4 ± 1.6	−1.8 ± 1.4	−1.1 ± 2.1

decreased approximately in proportion to the decrease in tidal volume, but thereafter V_D was unchanged. As a result there was no significant difference in V_D/V_T between the frequencies of 15 and 30 b.p.m., but thereafter V_D/V_T increased significantly.

There were no differences in cardiac output between 15 and 30 b.p.m., but there was a progressive decrease in output at greater frequencies. The peak, mean airway and end-inspiratory oesophageal pressures were least at a frequency of 30 b.p.m. At greater frequencies the lung failed to empty so that the pressures were again increased.

The experimental results in four dogs in group 2, when additional frequencies of 45, 300 and 450 b.p.m. were used, are shown in figures 4 and 5. Although a small end-expiratory pressure was present in one dog at the frequency of 45 b.p.m., the peak airway pressure was minimal at this frequency in the remaining three dogs. At the frequencies of 300

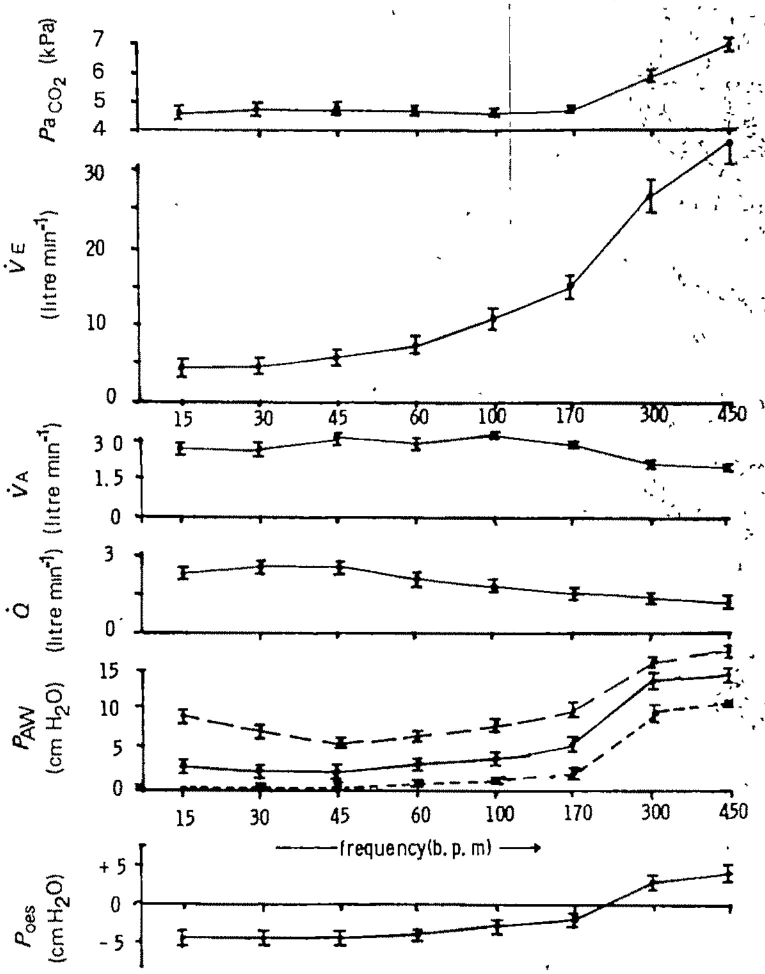


FIG. 4. Group 2: four dogs subjected to additional frequencies of ventilation. Changes in Pa_{CO_2}, minute volume ($\dot{V}$E), alveolar ventilation ($\dot{V}$A), cardiac output ($\dot{Q}$), airway pressure (P_{AW}), peak (– – –), mean (——), end-expiratory (- - - -) and oesophageal pressure (P_{oes}) with the increase in ventilation frequency.

and 450 b.p.m. the alveolar ventilation could not be maintained despite large increases in minute volume since physiological deadspace increased with the increase in end-inspiratory airway pressure. As a consequence Pa_{CO_2} increased to unacceptable values, the oesophageal pressure became positive and the cardiac output decreased.

DISCUSSION

The prime objective of the present studies was to examine the practical possibilities of ventilating the lungs at greater frequencies and smaller tidal volumes than normal in order to reduce the peak transpulmonary pressure difference required to maintain normal Pa_{CO_2}. The results suggested that in the dog the smallest alveolar pressures were achieved at a frequency of about 45 b.p.m.

The magnitude of the reduction in tidal volume which can be tolerated is obviously determined by the changes in apparatus, anatomical and physiological deadspace which accompany the changes in tidal volume. Although Jonzon and others (1971) and Erikson and others (1977) reported that adequate alveolar ventilation could be maintained at frequencies of 60–100 b.p.m. when the apparatus deadspace was negligible, the authors were not able to make accurate measurements of tidal volume alveolar pressure and gas exchange. Furthermore

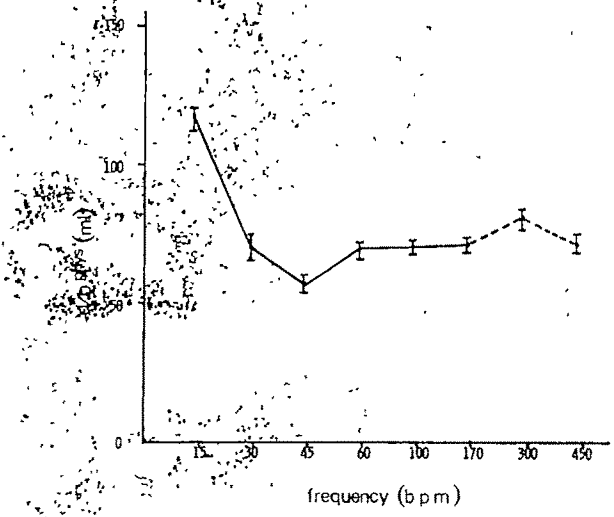


FIG. 5. Changes in physiological deadspace with increase in ventilation frequency in four dogs in group 2 subjected to additional frequencies of ventilation.

they used different ventilators and patient circuits to make comparisons between high and low frequencies. In other studies in humans and in dogs (Williams and Rayford, 1956; Severinghaus and Stupfel, 1957; Cooper, 1969; Hedenstierna and McCarthy, 1975; Lunn, Mapleson and Chilcoat, 1975), the apparatus deadspace was either included as a part of the ventilatory pathway or a nominal value (usually determined by water displacement) was deducted from the calculated physiological deadspace. Since the effective volume of the apparatus deadspace does not necessarily equal the volume determined by water displacement, the assumption of a fixed value may have introduced a variable error. Furthermore, the extra tidal volume required to compensate for the added deadspace would have increased the alveolar pressure and so might have affected the results.

In the present experiments the apparatus deadspace was negligible whilst the anatomical deadspace was reduced to the volume of the conducting airways below the tip of the insufflation catheter. Nunn, Campbell and Peckett (1959) showed in human cadavers that 55% of the total anatomical deadspace was above a point 6 cm above the carina, so it is reasonable to assume that the volume of the conducting airways below the tip of the insufflation catheter was about 50% of the normal anatomical deadspace in the dog.

In the first group of dogs an attempt was made to increase frequency whilst minute volume and inspiratory flow rate were maintained constant. The resulting decrease in tidal volume was accompanied by a progressive decrease in physiological deadspace. However, the reduction in deadspace was proportionately less than the decrease in tidal volume so that V_D/V_T increased.

In the second group of animals, when Pa_{CO_2} was kept constant by increasing minute volume, the reductions in tidal volume and physiological deadspace were less although the increase in V_D/V_T with frequency was of similar magnitude. The differences in tidal volume and Pa_{CO_2} between the two groups at the higher frequencies resulted in differences in mean airway pressure and cardiac output. For example, in the first group mean airway pressure at 100 b.p.m. was 71% of the value at 15 b.p.m. and cardiac output was unchanged, whereas in the second group mean airway pressure had increased to 154% and cardiac output had decreased to 76% of the values at 15 b.p.m. Thus, although the efficiency of ventilation as judged by V_D/V_T was decreased similarly in both groups at a frequency of 100 b.p.m., blood-gas homeostasis could be achieved only at the cost of greater airway pressures and a smaller cardiac output.

In group 2 further increases in frequency to 170 b.p.m. resulted in a further increase in V_D/V_T. At the two greatest frequencies, 300 and 450 b.p.m. (fig. 4), Pa_{CO_2} increased continually, indicating that the alveolar ventilation was no longer adequate to remove the carbon dioxide produced, despite the administration of very large minute volumes (26 litre min^{-1} and 34 litre min^{-1} respectively). At these frequencies the dogs were not in a steady state and much greater Pa_{CO_2} values would have been recorded if the observations had been delayed until a steady state had been reached.

It is apparent that the reduction in physiological deadspace is an important compensatory mechanism which helps to maintain alveolar ventilation in the slower range of frequencies. The peak and mean airway pressures are also reduced without impairment of cardiac output. However, at greater frequencies air trapping occurs and there is no further reduction in deadspace so that ventilation becomes progressively more inefficient, airway and oesophageal pressures increase and cardiac output decreases.

It is concluded that, in the normal dog with minimal apparatus and anatomical deadspace, respiratory frequencies up to 45 b.p.m. can be used to minimize peak alveolar pressures without producing a marked impairment in gas exchange or cardiac output. At a frequency of 60 b.p.m. there is an appreciable end-expiratory pressure and at greater frequencies there is an increase in airway pressure, a decrease in cardiac output and an increase in V_D/V_T. However, if these side-effects are tolerable, ventilation is practicable up to a frequency of 170 b.p.m. in the dog.

The experiments were carried out in dogs with normal lungs because it is difficult to produce a stable preparation with a low lung compliance. In low lung compliance states the tidal volume would be expected to encroach on the horizontal portion of the pressure–volume curve, so that a reduction in tidal volume would result in a greater percentage decrease in alveolar pressure compared with a normal lung. In a diseased lung a reduction in tidal volume might result in a greater impairment of gas exchange than was demonstrated in these studies. Furthermore, the dog has a relatively high compliance and low airway resistance when compared with man. Thus the optimal frequency of ventilation at which the smallest airway pressure is achieved may differ.

REFERENCES

Cooper, E. A. (1969). Physiological deadspace in passive ventilation. 2. Relationships with tidal volume, frequency, age and minor upsets of respiratory health. *Anaesthesia*, **22**, 199.

Erikson, I., Jonzon, A., Sedin, G., and Sjöstrand, U. (1977). The influence of the ventilatory pattern on ventilation, circulation and oxygen transport during continuous positive pressure ventilation. *Acta Anaesthesiol. Scand.* (Suppl.), **64**, 149.

Hedenstierna, G., and McCarthy, G. S. (1975). The effect of anaesthesia and IPPV with different frequencies on the anatomical and alveolar deadspace. *Br. J. Anaesth.*, **47**, 847.

Jonzon, A., Oberg, P. A., Sedin, G., and Sjöstrand, U. (1971). High frequency positive pressure ventilation by endotracheal insufflation. *Acta Anaesthesiol. Scand.* (Suppl.) XLIII.

Kelman, G. R., and Nunn, J. F. (1966). Nomograms for correction of blood P_{O_2}, P_{CO_2}, pH and base excess for time and temperature. *J. Appl. Physiol.*, **21**, 1484.

Loh, L., Sykes, M. K., and Chakrabarti, M. K. (1978). The assessment of ventilator performance. *Br. J. Anaesth.*, **50**, 63.

Lunn, J. N., Mapleson, W. W., and Chilcoat, R. T. (1975). Effects of changes of frequency and tidal volume of controlled ventilation. Measurements at constant arterial P_{CO_2} in dogs. *Br. J. Anaesth.*, **47**, 2.

Nunn, J. F., Campbell, E. J., and Peckett, B. W. (1959). Anatomical subdivisions of the volume of respiratory deadspace and effect of position of the jaw. *J. Appl. Physiol.*, **14**, 174.

Severinghaus, J. W., and Stupfel, M. (1957). Alveolar deadspace as an index of distribution of blood flow in pulmonary capillaries. *J. Appl. Physiol.*, **10**, 335.

Simons, R. S., and White, Y. S. (1976). Computer-facilitated measurements from cardiac output indicator dilution curves. *Br. J. Anaesth.*, **48**, 275.

Williams, M. A., and Rayford, C. M. (1956). Effect of variation of tidal volume on size of physiological deadspace in dogs. *J. Appl. Physiol.*, **9**, 30.

EFFETS CARDIORESPIRATOIRES DE LA VENTILATION SOUS PRESSION POSITIVE INTERMITTENTE A HAUTE FREQUENCE SUR LES CHIENS

RÉSUMÉ

On a procédé à une étude sur les effets cardiorespiratoires découlant de l'augmentation de la fréquence respiratoire sur deux groupes de chiens ventilés mécaniquement, à l'aide d'un système réduisant le nombre d'appareils nécessaires et minimisant l'espace mort anatomique. Dans un groupe, le débit cardiaque est resté constant lorsqu'on a augmenté la fréquence; alors que dans le second groupe, on a augmenté le débit cardiaque pour que la Pa_{CO_2} reste normale. La réduction du volume courant lors de l'augmentation de la fréquence a éte accompagnée d'une diminution de l'espace mort physiologique. Quoi qu'il en soit, la réduction de l'espace mort a été proportionnellement moindre que la diminution du volume courant, de sorte que le rapport espace mort/volume courant a augmenté. Les pressions de pointe dans les passages d'air ont été minimales à la fréquence de 45 respirations/min. Aux fréquences supérieures à 60 respirations/min, les poumons n'ont pas pu se vider, de sorte que les pressions de pointe des passages d'air ont augmenté et que le débit cardiaque a diminué.

KARDIORESPIRATORISCHE WIRKUNGEN VON INTERMITTIERENDER POSITIVER DRUCKBELÜFTUNG FÜR HOHE ATEMFREQUENZ BEI HUNDEN

ZUSAMMENFASSUNG

Die kardiorespiratorischen Effekte der Erhöhung der Atemfrequenz wurden in 2 Gruppen von Hunden untersucht, die mechanisch mit einem System beluftet wurden, durch das Apparate ebenso wie der anatomische Totraum minimalisiert wurde. In einer Gruppe war das Minutenvolumen konstant, während die Frequenz erhoht wurde; in der zweiten Gruppe wurde das Minutenvolumen erhöht, um Pa_{CO_2} normal zu halten. Die Verringerung des Atemvolumens bei erhöhter Frequenz war von einer Verringerung des physiologischen Totraums begleitet. Allerdings war die Totraumverringerung proportional geringer als die Verringerung des Atemvolumens, so dass das Verhaltnis Totraum/Atemvolumen anstieg. Die Luftweg-Spitzendrucke waren minimal bei einer Frequenz von 45 b.p.m. Bei Frequenzen von 60 b.p.m. und daruber leerte sich die Lunge nicht, so dass die Luftweg-Spitzendrucke anstiegen und das Herzminutenvolumen sank.

EFECTOS CARDIORESPIRATORIOS DE LA VENTILACION DE PRESION POSITIVA INTERMITENTE DE ALTA FRECUENCIA EN EL PERRO

SUMARIO

Se llevó a cabo una investigación de los efectos cardiorespiratorios de la creciente frecuencia respiratoria en dos grupos de perros ventilados mecánicamente con un sistema que minimiza el espacio muerto anatómico y del aparato. En un grupo, el volumen por minuto era constante mientras aumentaba la frecuencia; en el segundo grupo, se aumentó el volumen por minuto para mantener un Pa_{CO_2} normal. La reducción del volumen respiratorio con una frecuencia creciente se acompañó de una reducción del espacio muerto fisiológico. Sin embargo, la reducción del espacio muerto fue en proporción menor que la disminución del volumen respiratorio de manera que la relación espacio muerto/volumen respiratorio aumentó. Las presiones tope de las vías respiratorias fueron mínimas en una frecuencia de 45 b.p.m. En frecuencias de 60 b.p.m. ó más, el pulmón dejó de vaciarse de modo que les presiones tope de las vías respiratorias aumentaron y el ritmo cárdiaco disminuyó.

Br. J. Anaesth. (1980) **52**, 483

DEATH ASSOCIATED WITH ANAESTHESIA IN FINLAND

M. Hovi-Viander

SUMMARY

The mortality associated with 338 934 procedures carried out in 1975 in 100 Finnish hospitals is reported. There were 626 deaths (1/541 or 0.18%). Mortality during the procedure was 1/5059 (0.02%). Twelve patients died primarily of anaesthesia during the procedures and 55 patients later (total anaesthetic mortality 1/5059, 0.02%). The frequency of cardiac arrest was 1/3808 (0.03%). Most of the 67 anaesthetic deaths were caused by inadequacy of management of fluid balance (17 patients) or respiratory insufficiency (15 patients). There were 12 deaths from cardiac complications, five each from technical errors and inadequate supervision after operation. The primary disease was responsible for approximately 72% of the reported deaths.

Death associated with anaesthesia was reported first in 1848 following the demise of Hannah Greener during chloroform anaesthesia (Phillips and Capizzi, 1974). Since then several studies have been conducted into such deaths (Pohjola et al., 1968; Holland, 1970; Marx, Mateo and Orkin, 1973; Bodlander 1975). However, it is still difficult to evaluate precisely the relative contribution of the procedure, the primary disease and other factors. In most instances, death during anaesthesia is not caused only by the anaesthetic (Holland, 1970; Anaesthetics Mortality Committee (S.A.), 1976), since both the operative procedure and the underlying disease cause physical and mental stress. The risk associated with the operative or other procedure involves several factors: the patient's physical status and disease, age and the adequacy of preoperative preparation and therapy. The urgency and extensiveness of surgery, the methods used during surgery and anaesthesia and the abilities of the surgeon and the anaesthetist contribute also to the total risk (Goldstein and Keats, 1970; Andersen, 1971).

During the past 15 yr there have been major changes in anaesthetic techniques and an increase in the number of anaesthetists and other specialized hospital personnel. Nowadays indications for surgery are wider and the number of extensive operations, especially on the elderly, has increased. The establishment of intensive care units has altered the prognosis of critically ill patients. The present study was undertaken to assess the effect of these changes on the mortality caused by complications associated with anaesthesia in Finnish hospitals in 1975 compared with that observed in 1963 (Pohjola et al., 1968).

METHODS

Deaths in Finnish hospitals in 1975 were abstracted from the Patients' Departure Register kept by the National Board of Health in Finland. Lists of these patients were sent by the National Board of Health to all Finnish hospitals, who were asked to remit the medical records of patients who had undergone anaesthesia or an operation, or both, or investigative/therapeutic procedures requiring anaesthesia in the following categories:

(1) Patients who had died within 3 days of anaesthesia or other procedure—473 (75.6%) patients.

(2) Patients who had suffered cardiac arrest and had been resuscitated during anaesthesia but who had died more than 3 days later—five (0.8%) patients.

(3) Patients in whom anaesthesia or other procedure was associated with death occurring later (inadequate care before, during or after operation, pulmonary aspiration, technical mishap, etc.)—148 (23.6%) patients.

Information from the clinical reports detailing the patients' physical status (classified according to the ASA classification (American Society of Anesthesiologists, 1963), therapy before, during and after operation, the nature and urgency of the procedures, the various complications and their treatment and other selected information was recorded on a computer-compatible proforma. A general assessment of the clinical reports was made concerning the patients' medical history during their entire stay in hospital. Three other specialist anaesthetists were consulted about difficult cases.

Marja Hovi-Viander, M.D., Department of Anaesthesiology, University of Turku, Finland.
Correspondence to: Ylännekatu 33, Turku 52, Finland.

0007-0912/80/050483-07 $01.00

© Macmillan Journals Ltd 1980

The 100 hospitals under study were sent a questionnaire concerning, among other things, surgical and anaesthetic techniques, the number of procedures, operative beds and intensive care units and the number of medical specialists. Background information obtained in this way and from the National Board of Health allowed an overall view of the anaesthetic and surgical routines.

RESULTS

There were 626 cases from 68 Finnish hospitals or clinics (University clinics were regarded as separate hospitals). In 32 hospitals there were no cases fulfilling any of the criteria of the present study, but information concerning the anaesthetic and surgical techniques was obtained. These 100 hospitals represent all those Finnish hospitals where a typical range of anaesthetic and operative procedures was carried out.

The total number of operations in the hospitals under study during 1975 was 338 934. This included 42 145 (12.4%) emergency operations which were most frequent (24 980 (59.3%)) in University Hospitals. In the hospitals studied there were 220 anaesthetists (133 specialists) and 1124 other doctors who regularly performed operations, investigations or therapeutic procedures requiring anaesthesia (these doctors did not administer anaesthetics). The total number of surgical beds in the hospitals was 8500 of which 1.1% were in intensive care or intensive observation units.

Distribution according to age, the quality of procedures and preoperative condition of the patient

The age distribution of the patients whose death was associated with anaesthesia or operation is shown in figure 1. Of the 273 women and 353 men, 65.1% were more than 60 yr and 7.5% less than 16 yr.

The 626 patients had undergone 921 procedures of which 889 (maximum three per patient) were analysed statistically (table I). More than half of the procedures (62.4%) were regarded as extensive or major—for example cholecystectomy or a more extensive procedure. Of all the operations on adult patients 348 (39.2%) were abdominal, 88 (9.9%) thoracic or vascular, 60 (6.8%) orthopaedic or plastic and 54 (6.1%) neurosurgical. Fifty-six (6.3%) were investigations or therapeutic procedures not involving operations and 63 (7.1%) were procedures on children (table I). More than half (56.5%) of all procedures were undertaken as an emergency. One hundred and thirty-nine patients were re-operated upon during their last stay in hospital because of a complication such as postoperative bleeding or an

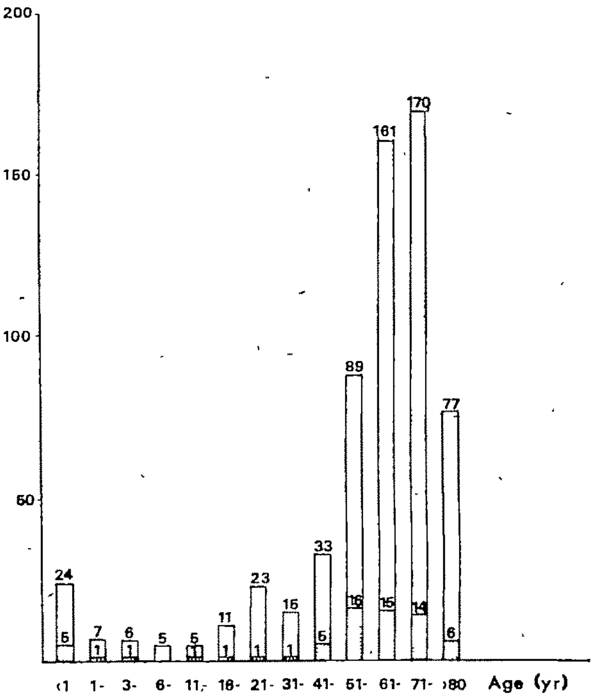


FIG. 1. Age distribution of the patients who died. The stippled columns represent deaths occurring during the procedure.

TABLE I. *Procedures performed on the 626 patients*

Procedure	Total	%
Paediatric operations and other procedures on children	63	7.1
Neurosurgical	54	6.1
Pulmonary	21	2.4
Heart and thoracic–vascular	19	2.1
Non-thoracic vascular	69	7.8
Acute abdominal	231	26.0
Elective abdominal	117	13.2
Urological	30	3.4
Gynaecological	4	0.4
Orthopaedic and plastic surgical	60	6.8
Emergency operations for trauma in adults	18	2.0
Amputations	42	4.7
Other operations	68	7.6
Incisions, revisions, sutures etc.	28	3.1
Drainages and cannulations	9	1.0
Therapeutic and investigative procedures	56	6.3
Total	889	100

intra-abdominal emergency. The majority of these re-operations were undertaken as an emergency.

The condition of 491 patients (78.4%) before their first procedure was bad or moribund: 433 (69.2%) were ASA grade IV–V, as were 55 (88.1%) of 67 patients who died during the procedure. As a general rule the ASA grade deteriorated as the number of procedures increased (table II).

TABLE II. *Physical status of 626 patients according to ASA classification (number; per cent in parentheses)*

Status	1st procedure	2nd procedure	3rd procedure
I	8 (1.2)	0 (0)	0 (0)
II	43 (6.9)	1 (0.5)	0 (0)
III	142 (22.7)	25 (12.8)	3 (4.4)
IV	296 (47.3)	123 (63.1)	33 (51.5)
V	137 (21.9)	46 (23.6)	30 (44.1)
Total	626 (100)	195 (100)	68 (100)

Most of the 626 patients apparently received adequate treatment before operation. The commonest deficiencies in preoperative therapy were inadequate management of fluid balance and respiratory insufficiency. Two hundred and fifty-three patients were treated in intensive care units, mainly in the University or Central Hospitals.

Cardiac arrest associated with the procedure

Cardiac arrest during or immediately after the procedure occurred in 89 patients. Resuscitation was successful initially in 22 (24.7%) of these. Most of these particular patients had severe surgical pathology and many of them had pre-existing cardiac disease. The majority of the 89 cardiac arrests took place during the maintenance of anaesthesia.

Factors contributing to death

Anaesthesia was the primary cause of death in 67 (10.7%) cases and death was attributed to surgery in 73 (11.7%). The primary disease caused the death of 450 (71.9%) patients and the other deaths (36 (5.7%)) were attributable to miscellaneous causes (table III). However, in most of the deaths multiplicity of factors was present. Anaesthesia was estimated to be an extra contributing factor in 173 deaths, surgery in 103, the primary disease in 59 and other factors in 291 deaths. One hundred and fifty-eight patients had malignant disease, which was the main cause of death in 97. Of the patients who died of the primary disease 47 had brain damage and 17 of these 47 had other injuries. Mesenteric thrombosis was the primary disease contributing to death in 31 patients; thoracic or abdominal aortic aneurysms in 13. Congenital anomalies or heart defects (17 patients) or various injuries (nine patients) were the most common primary causes of death in children.

TABLE III. *Classification of causes of deaths associated with anaesthesia and surgery or investigations/therapeutic procedures requiring anaesthesia. * Counted per 338 934 procedures. † Includes five patients with cause of death unknown*

Main cause of death	Patients	%	Frequency*	%
Anaesthesia	67	10.7	1/5059	0.02
Surgery	73	11.7	1/4643	0.02
Disease	450	71.9	1/753	0.13
Other causes	36†	5.7	1/9415	0.01

Patients in whom anaesthesia was the main cause of death (67 *patients*)

The ages of those patients whose death was caused mainly by anaesthesia ranged from 2 yr to 92 yr. These 67 patients had undergone 85 procedures including 76 operations of which 54 (63.5%) were classed as being extensive, 68.7% were in ASA grades IV–V before the first procedure and this percentage increased to 93.3% and 100% before the second and the third procedures. Twelve patients died during the procedure, four during induction of anaesthesia, four during maintenance, three while awakening and one patient on removal to the recovery room. In 24 patients there was a probable overdose of anaesthetic drugs in relation to their physical status and age. The unfavourable effects of overdosage were often associated with the poor condition of the patient and deficiencies in preoperative therapy. Inadequate care and supervision after operation probably caused one death and contributed to five others. Of the anaesthetic deaths 32 (48%) were caused by shortcomings in the management of the fluid balance or by respiratory insufficiency (table IV). Most of these 32 patients suffered from trauma or significant intra-abdominal disease. Twelve patients died of cardiac complications including myocardial infarction (seven) caused probably by mismanagement during anaesthesia. One patient died of a dextran-induced anaphylactoid reaction during spinal anaesthesia for prostatectomy (table IV). One patient with asthma died of bronchospasm during general anaesthesia induced with thiopentone and one patient died after surgery of an asthmatic attack which began during

TABLE IV. *Causes of death to which anaesthesia contributed primarily (ACD). *Probably caused by mismanagement during anaesthesia*

	Cause of complication	Patients	% of ACD	% of Total
I	Anaphylaxis (Dextran)	1	1.5	0.2
II	Aspiration*	5	7.5	0.8
III	Asthmatic attack	2	3.0	0.3
IV	Respiratory insufficiency	15	22.4	2.4
V	Insufficient management of fluid balance:	17	25.3	2.7
	Before operation	4		
	During operation	5		
	Death from shock	8		
VI	Cardiac dysfunction	12	17.9	1.9
	Vagal arrhythmia	1		
	Postoperative cardiac arrest	1		
	Acute cardiac failure	3		
	Myocardial infarction*	7		
VII	Anaesthetic deaths with unknown causes:	8	11.9	1.2
	Anaesthesia, surgery and primary disease contributing to	1		
	Partly unknown causes	5		
	Entirely unknown causes	2		
VIII	Inadequate postoperative supervision	1	1.5	0.2
IX	Overhydration + no indication for anaesthesia (cardiac death)	1	1.5	0.2
X	Technical complications	5	7.5	0.8
	Intubation failed	1		
	Error in connecting anaesthetic machine	1		
	Ventilator function	2		
	Rupture of subclavian artery (subclavian vein cannulation)	1		
Total		67	100	10.7

the operation. Technical complications caused five anaesthetic deaths. One patient died after unsuccessful intubation, three because of technical errors in respirator therapy. One died of haemothorax and shock caused by the rupture of the subclavian artery after subclavian vein cannulation. Overhydration, cardiac failure, hypoxia and wrong indication for anaesthesia probably caused one death. Of the eight deaths in which anaesthesia contibuted primarily, the exact cause of death was totally or partly unknown because of insufficient information in the clinical reports.

Time of death

Of the 626 patients 139 (22.2%) died on the day of the procedure and 67 during it. Twelve of the 67 died primarily because of anaesthesia. One hundred and seventy-six (28.1%) patients died 1 day after the last procedure and 108 (17.3%) patients 2–3 days later. One hundred and twenty (19.2%) patients died 4–14 days after the last procedure and 83 (13.2%) patients more than 2 weeks afterwards. Intensive therapy appeared to be a major factor in delaying death.

Of all the patients, six died during induction of anaesthesia, 42 during the procedure, 11 during the awakening period and two on arrival in the recovery room, where 10 more patients died. Three hundred and sixty-eight patients died in the ward, 186 in the intensive care unit and one in the x-ray department.

Frequency of deaths

In this study the frequency of deaths caused by reported complications was 626/338 934 (0.18%) (table V). The primary disease was the main contributor to death in more than two-thirds of cases.

TABLE V. *Death and cardiac arrest associated with anaesthesia and surgery or investigations/therapeutic procedures requiring anaesthesia. * Counted per 338 934 procedures. † Includes 12 anaesthetic deaths. ‡ One patient had two cardiac arrests associated with the procedure*

Complication	Patients	%	Frequency*	%
Total deaths associated with procedures	626	100	1/541	0.18
Total mortality during the procedure	67†	10.7	1/5059	0.02
Cardiac arrests associated with the procedure	89‡	14.2	1/3808	0.03

The frequency of death during the procedure was 1/5059 (0.02%) and of cardiac arrest associated with the procedure 1/3808 (0.03%). There were deaths primarily attributable to anaesthesia in 1/5059 (0.02%) procedures. Only 12/67 anaesthetic deaths took place during the procedure.

Postmortem findings

A postmortem examination was performed on 495 (79.1%) patients. There were great differences in the number and nature of the postmortems among the hospitals. A discrepancy between the clinical and postmortem diagnoses or that written on the death certificate was found in 251 instances.

Standard of therapy

The therapy as a whole was estimated to be adequate in 517 (82.6%) patients and inadequate in 73 (11.7%). It was impossible to classify the standard in the remainder.

DISCUSSION

This report includes all the deaths in connection with operation and investigations or therapeutic procedures requiring anaesthesia in Finnish hospitals in 1975. Compared with previous studies, the concept of operative mortality in this study has been widened to include those patients who had any defect or complication of their anaesthetic or surgical care which contributed to death more than 3 days after the procedure, a feature omitted from many earlier studies (Pohjola et al., 1968; Holland, 1970; Bodlander, 1975; Harrison, 1978). This group of patients accounted for 23.6% of the deaths in the present study. They were mainly old people, many of whom were treated in the intensive care unit and who died of infection after operation—a common cause of death in such patients (Lehmann, 1971; Pessi, 1973). Because of the differences in patient selection, comparison with other published series is difficult.

Mortality during operations (1/1800–1/2500) recorded in 1963 in Finnish hospitals (Pohjola et al., 1968) decreased to 1/5059 in 1975 in spite of the fact that both the range of surgery and the mean age of the patients increased. The frequency of primary anaesthetic deaths (0.02%) in the present study is comparable to that (0.01%–0.08%) of anaesthetic deaths mentioned in recent literature (Minuck, 1967; Holland, 1970; Marx, Mateo and Orkin, 1973; Bodlander, 1975; Harrison, 1978) although the frequency presented in this study includes the anaesthetic deaths associated with investigations or therapeutic procedures requiring anaesthesia.

Half of the deaths in this study occurred in patients who underwent emergency procedures. These included two-thirds of all deaths during the procedure. About 65% of the operative deaths were associated with patients older than 60 yr of age. This is in agreement with several studies indicating that mortality associated with operations increases after the age of 60 yr (Stahlgren, 1961; Renck, 1969; Marx, Mateo and Orkin, 1973; Miller, Marlar and Silvay, 1977). The physical status of the patients and the type of operation are, however, among the most important contributing factors in operative mortality (Pohjola et al., 1968; Holland, 1970; Marx, Mateo and Orkin, 1973; Harrison, 1978) and this was clear in the present study.

In 1963 in Finnish hospitals 16.7% of the deaths during anaesthesia occurred during the induction and 53.8% in the awakening period (Pohjola et al., 1968). These periods are especially liable to accidents and errors in management. An improvement in the standard of anaesthesia can be seen from the corresponding figures, 9% and 19.4% respectively, in the present study, and is partly because of an increase in the number of specialist anaesthetists and nurses making it possible to supervise and treat patients more effectively during recovery. The same trend to a decrease in mortality during induction and recovery has been reported by others (Holland, 1970; Bodlander, 1975; Harrison, 1978).

The most common causes of anaesthetic death in this study were similar to those observed earlier (Gordh, 1965, 1974; Gebbie, 1966; Harrison, 1968, 1978; Holland, 1970; Cascorbi and Gravenstein, 1974; Bodlander, 1975)—inadequate control of fluid balance and lung function, relative overdosage in critically ill patients and cardiac failure. Aspiration of stomach contents to the tracheobronchial tree as a cause of mortality continues to be a problem. Rarer causes of primary anaesthetic deaths in the present study were anaphylaxis induced by dextran and technical complications, which are described in recent literature (Bauer and Östling, 1970; Kohen et al., 1970; Ring and Messmer, 1976; Fanous, Gray and Felmingham, 1977; Furhoff, 1977; Sears and Bocar, 1977; Spurring and Shenolikar, 1978). It has been suggested (Bruce and Wingard, 1971) that general anaesthesia might protect the patient from a severe anaphylactic reaction, but Gordh and Mostert (1978) have recently criticized this opinion. They emphasize that anaphylaxis may occur in association with any mode of anaesthesia, and remind us in addition of the importance of careful control of ventilators and other anaesthetic equipment during all periods of anaesthesia, which is borne out in the present study.

In the majority of cases the severe primary disease was the main cause of death and only a small number of all the complications could have been prevented. The frequency of anaesthetic deaths in Finland has decreased by about half in 12 yr, and is now 1/5059. Therefore anaesthetic procedures can nowadays be regarded as relatively safe, although a certain risk must be present always.'

ACKNOWLEDGEMENTS

I am grateful to Professor Matti Vapaavuori, M.D., and to Professor Tapani Tammisto, M.D., for constructive criticism and advice during this study. I thank my colleague Matti Salo, M.D., for help in analysing the difficult cases and in revising the manuscript.

Invaluable help of the National Board of Health in Finland in providing the material under study is gratefully appreciated.

This study was supported financially by grants from the Paulo Foundation and from the Cultural Foundation of Finland (The Fund of Professor Sauli Viikari).

REFERENCES

Anaesthetics Mortality Committee (S.A.) (1976). Anaesthetics deaths in South Australia. *Med. J. Austr.*, **10**, 4.

Andersen, B. (1971). Praeoperative vurdering af operativ risiko (English summary). Thesis. *F.A.D.L.'s Forlag, Odense.*

American Society of Anesthesiologists (1963). New classification of physical status. *Anesthesiology*, **24**, 111.

Bauer, Å, and Östling, G. (1970). Dextran-induced anaphylactoid reactions in connection with surgery. *Acta Anaesthesiol. Scand.* (Suppl.) **37**, 182.

Bodlander, F. M. S. (1975). Deaths associated with anaesthesia. *Br. J. Anaesth.*, **47**, 36.

Bruce, D. L., and Wingard, D. W. (1971). Anesthesia and the immune response. *Anesthesiology*, **34**, 271.

Cascorbi, H. F., and Gravenstein, J. S. (1974). Silent death. *Anesthesiology*, **40**, 319.

Fanous, L. H., Gray, A., and Felmingham, J. (1977). Severe anaphylactoid reactions to dextran 70. *Br. Med. J.*, **2**, 1189.

Furhoff, A.-K. (1977). Anaphylactoid reaction to dextran. A report on 133 cases. *Acta Anaesthesiol. Scand.*, **21**, 161.

Gebbie, D. (1966). Anaesthesia and death. *Can. Anaesth. Soc. J.*, **13**, 390.

Goldstein, A. jr, and Keats, A. S. (1970). The risk of anesthesia. *Anesthesiology*, **33**, 130.

Gordh, T. (1965). Complications in connection with local anaesthesia. *Acta Anaesthesiol. Scand.*, (Suppl.) **16**, 137.

—— (1974). Anestesiologiska komplikationer. *Opusc. Med.* (Suppl.), **38**, 1.

—— Mostert, J. W. (1978). Anesthetic accidents: case studies. *Int. Anesthesiol. Clin.*, **16**, 1.

Harrison, G. G. (1968). Anesthetic contributory death—its incidence and causes. *S. Afr. Med. J.*, **42**, 514 and 544.

—— (1978). Death attributable to anaesthesia. A 10-year survey (1967–1976). *Br. J. Anaesth.*, **50**, 1041.

Holland, R. (1970). Special committee investigating deaths under anaesthesia: Report on 745 classified cases, 1960–1968. *Med. J. Austr.*, **21**, 573.

Kohen, M., Mattikow, M., Middleton, E. jr, and Butsch, D. W. (1970). A study of three untoward reactions to dextran. *J. Allergy*, **46**, 309.

Lehmann, Ch. (1971). Intensivbehandlung beim älteren Patienten; in *Anaesthesiologie und Wiederbelebung*, p. 55, Berlin: Springer-Verlag.

Marx, G. F., Mateo, C. V., and Orkin, L. R. (1973). Computer analysis of postanesthetic deaths. *Anesthesiology*, **39**, 54.

Miller, R., Marlar, K., and Silvay, G. (1977). Anesthesia for patients aged over ninety years. *N.Y. State J. Med.*, **77**, 1421.

Minuck, M. (1967). Death in the operating room. *Can. Anaesth. Soc. J.*, **14**, 197.

Pessi, T. (1973). Experiences gained in intensive care of surgical patients. *Ann. Chir. Gynn. Fenniae*, **62** (Suppl. 185), 1.

Phillips, O. C., and Capizzi, L. S. (1974). Public health aspects of critical care medicine and anesthesiology. Anesthesia mortality. *Clin. Anesth.*, **10**, 220.

Pohjola, E., Tammisto, T., Korkeila, J., Isotalo, A., and Varis, W. (1968). Deaths associated with anaesthesia and surgery in Finnish Hospitals in 1963 (English summary); in *Health Services Research by the National Board of Health in Finland*, no. 6, Helsinki.

Renck, H. (1969). The elderly patient after anaesthesia and surgery. *Acta Anaesthesiol. Scand.* (Suppl.) **34**, 1.

Ring, J., and Messmer, K. (1976). Anaphylaktoide Reaktionen nach Infusion kolloidaler Volumenersatzmittel. *Pädiat. Praxis*, **17**, 283.

Sears, B. E., and Bocar, N. D. (1977). Pneumothorax resulting from a closed anesthesia ventilator port. *Anesthesiology*, **47**, 311.

Spurring, P. W., and Shenolikar, B. K. (1978). Hazards in anaesthetic equipment. *Br. J. Anaesth.*, **50**, 641.

Stahlgren, L. H. (1961). An analysis of factors which influence mortality following extensive abdominal operations upon geriatric patients. *Surg. Gynecol. Obstet.*, **113**, 283.

DECES CONSECUTIF A UNE ANESTHESIE EN FINLANDE

RESUME

On décrit dans cet article la mortalité associée à 338 934 cas traités en 1975 dans 100 hôpitaux finlandais. Il y a eu 626 décès (1/541 ou 0,18%). La mortalité pendant l'intervention a été de 1/5059 (0,02%). Douze patients sont morts surtout du fait de l'anesthésie pendant les interventions et 55 autres plus tard (mortalité totale par suite d'anesthésie 1/5059 (0,02%)). La fréquence d'arrêt cardiaque a été de 1/3808 (0,03%). La plus grande partie des 67 décès dus à l'anesthésie est imputable à la régulation inadéquate de l'équilibre des fluides (17 patients) ou à l'insuffisance respiratoire (15 patients). Il y a eu 12 décès découlant de complications cardiaques, cinq par suite d'erreurs techniques et cinq par suite de surveillance insuffisante après l'intervention. La maladie primaire est responsable d'environ 72% des cas de décès signalés.

TOD DURCH NARKOSE IN FINNLAND

ZUSAMMENFASSUNG

Es wird uber die Sterblichkeit bei 338 934 Verfahren berichtet, die im Jahre 1975 in 100 finnischen Krankenhausern durchgefuhrt wurden. Es gab dabei 626 Todesfälle (1/541 oder 0,18%). Die Sterblichkeit wahrend des Verfahrens betrug 1/5059 (0,02%). Zwolf Patienten primär

durch die Narkose während der Verfahren, und 55 Patienten starben später (gesamte Narkose-Sterblichkeit 1/5059 oder 0,02%). Die Häufigkeit von Herzstillstand betrug 1/3808 (0,03%). Die meisten der 67 Narkose-Todesfälle wurden durch unzureichende Aufrechterhaltung des Flüssigkeitsgleichgewichtes verursacht (17 Patienten), oder durch respiratorische Unzulänglichkeiten (15 Patienten). Es gab 12 Todesfälle durch Herzkomplikationen, je fünf durch technische Fehler oder durch unzureichende Überwachung nach der Operation. Etwa 72% der gemeldeten Todesfälle waren auf die ursprüngliche Krankheit der Patienten zurückzuführen.

MORTALIDAD ASOCIADA CON LA ANESTESIA EN FINLANDIA

SUMARIO

Se informa sobre la mortalidad respecto de 338 934 administraciones llevadas a cabo en 1975 en 100 hospitales finlandeses. Hubo 626 decesos (1/541 ó 0,18%). La mortalidad durante la administración fue de 1/5059 (0,02%). Doce pacientes murieron originalmente a causa de la anestesia en el curso de la administración y 55 pacientes más tarde (mortalidad total por anestesia 1/5059 ó 0,02%). La frecuencia de paros cárdiacos era de 1/3808 (0,03%). La mayoría de los 67 decesos por anestesia fueron causados por la impropiedad de la gestión del equilibrio de fluidos (17 pacientes) o por la insuficiencia respiratoria (15 pacientes). Hubo 12 decesos debidos a complicaciones cárdiacas, cinco de los cuales ocurrieron a raíz de errores técnicos y de control inadecuado después de la operación. La enfermedad original causó aproximadamente un 72% de los decesos registrados.

Br. J. Anaesth. (1980), **52**, 491

CLINICAL STUDIES OF GAS EXCHANGE DURING VENTILATORY SUPPORT—A METHOD USING THE SIEMENS-ELEMA CO_2 ANALYZER

S. G. Olsson, R. Fletcher, B. Jonson, L. Nordström and O. Prakash

SUMMARY

We describe a new portable infra-red analyser for use with the Siemens–Elema Servo ventilator. The sensor head constitutes a Y-piece connecting the patient to the ventilator tubing, and gives instant carbon dioxide determination. It is based upon simple principles that can be realized with modern techniques, offering for instance freedom from interference by anaesthetic gases, and eliminating the need for calibration. A non-zero inspired carbon dioxide concentration interferes with the measurements. Integration of the carbon dioxide signal with the flow signal from the Servo ventilator yields data about carbon dioxide excretion, and additional calculation yields V_D/V_T if Pa_{CO_2} is known. The accuracy of determination of end-tidal carbon dioxide and carbon dioxide elimination was found to be adequate for research purposes, and that of V_D/V_T for clinical purposes. The device is considered to be of value in the operating theatre and intensive care unit, for monitoring, as a guide to ventilatory needs, and for the investigation of the magnitude and causes of increased deadspace.

When ventilatory support is required, control of gas exchange is at least as important as ventilation itself. The following equations show some factors that govern the maintenance of Pa_{CO_2}:

$$Pa_{CO_2} = \frac{\dot{V}CO_2}{\dot{V}A} \times k \qquad (1)$$

$$\dot{V}A = \dot{V}T - \dot{V}D \qquad (2)$$

It is assumed that equilibrium occurs between alveolar and arterial PCO_2. $\dot{V}CO_2$ = carbon dioxide production, $\dot{V}A$ = alveolar ventilation, $\dot{V}T$ = total ventilation and $\dot{V}D$ = ventilation of physiological deadspace. k is a factor converting carbon dioxide fraction to PCO_2.

In the absence of lung disease, end-tidal PCO_2 (PE'_{CO_2}) closely reflects Pa_{CO_2} (Galdston, Benjamin and Hurewitz, 1951; Collier, 1955; Dahlgren and Symreng, 1974), and adequate Pa_{CO_2} is generally maintained with ordinary ventilation. When this is not the case the analysis of mechanisms involved is aided by knowledge of VCO_2 and the various fractions of deadspace. Suitable systems for measurement of PE'_{CO_2}, $\dot{V}CO_2$ and $\dot{V}D$ have in the past been bulky, cumbersome and expensive. This paper presents an unobtrusive device for making these measurements in the intensive care unit and operating theatre. The basis of the measurements is the integration of signals for carbon dioxide concentration of expired gas, and expiratory flow. This yields much additional information, and the CO_2 Analyzer also offers advantages over previous devices in compactness, ease of handling, accuracy and freedom from errors caused by anaesthetic gases.

APPARATUS AND WORKING PRINCIPLES

The Servo ventilator 900 or 900 B (Ingelstedt et al., 1972) produces an expiratory flow signal and the carbon dioxide signal comes from the CO_2 Analyzer 930 described below (both from Siemens–Elema AB, Solna, Sweden). The CO_2 Analyzer is designed to operate with the ventilator, which provides a flow signal and power and timing pulses.

The carbon dioxide sensor (fig. 1) works on the principle of absorption of infra-red radiation from a broad spectrum IR emitter (fig. 2). The radiation passes via sapphire glass windows through a Y-piece connecting the patient to the ventilator tubing. The Y-piece offers a negligible resistance to flow (0.8 cm H_2O litre^{-1} s) at a flow rate of 0.5 litre s^{-1} and 1.6 at 1 litre s^{-1}). Its deadspace is smaller than that of the ordinary Y-piece that it replaces. Part of the radiation is absorbed by the windows which are thereby heated, preventing condensation. Carbon dioxide molecules in the gas cause further absorption

---

S. G. Olsson, Siemens–Elema Company, Solna, Sweden. R. Fletcher, F.F.A.R.C.S.; L. Nordström, M.D.; Department of Anaesthesia, University Hospital, Lund, Sweden. B. Jonson, M.D., Department of Clinical Physiology, University of Lund, Sweden. O. Prakash, M.D., Thoraxcenter, Erasmus University, Rotterdam, The Netherlands.

0007-0912/80/050491-09 $01.00

© Macmillan Journals Ltd 1980

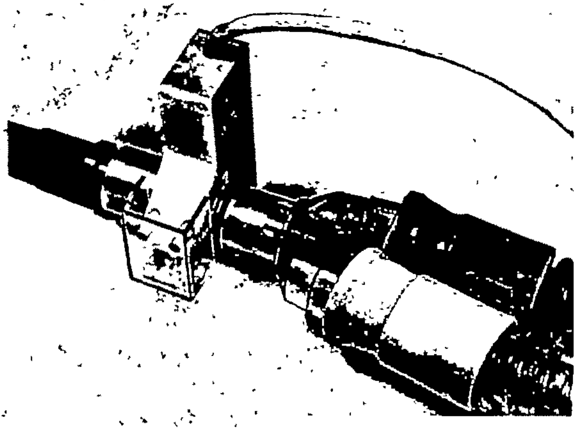


FIG. 1. Carbon dioxide sensor and cuvette.

of IR radiation of specific wavelengths. The radiation is then mechanically chopped at a frequency of 180 Hz. An interference filter transmits only light with a wavelength of 4.2 μm at which carbon dioxide has a main absorption peak. The band-width is 0.07 μm. The chopped and filtered radiation is received by a photoelectric Ge-As-sensor, the signal of which is amplified.

The signal oscillates between one value when the chopper is closed and another when it is open. Thus the chopper generates a carrier frequency that is modulated by the transmitted radiation. In this way problems inherent in detection of small signals superimposed upon large drifting ones are solved.

The amplitude of the oscillations generated by the chopper reflects transmitted pulsed light, which is a function of carbon dioxide absorption within the gas. Irrelevant factors such as the amount of emitted radiation, its absorption within the windows and the temperature of the IR detector also affect the signal. This problem is eliminated by the signal processor to which the signal is transmitted after amplification.

The signal processor (fig. 2) demodulates the signal by an amplifier that is phase-locked to the chopper signal. After demodulation a signal U corresponds to the amount of light received. At the end of inspiration there is no carbon dioxide in the sensor head. The signal at this moment (U_I) is sampled and held, to be used as a reference for the following expiration. An analog divider gives the quotient U/U_I. In the absence of carbon dioxide, when $U = U_I$, the output signal is standardized to 1 arithmetic unit. The division by U_I corrects for changes in the amount of emitted light, absorption in the windows, the sensitivity of the IR detector and primary amplification of the signal. If for example dirt, or a droplet of sputum, lands on one of the windows, this will only influence the current expiration. For the following expiration a new U_I will restore correct amplification.

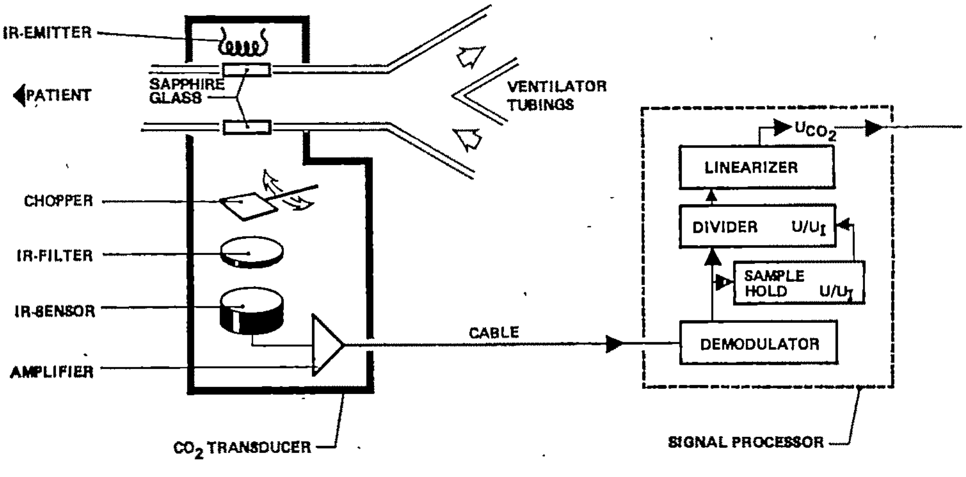


FIG. 2. The carbon dioxide transducer and initial part of circuitry within the CO_2 Analyzer 930. A beam of infra-red radiation passes through the expired gas via sapphire windows in a detachable Y-piece connecting the patient to the ventilator tubing. The beam is mechanically chopped, filtered and sensed by a photoelectric sensor. The signal is amplified and transmitted to the Analyzer. The original signal is processed to yield a signal, U_{CO_2}, that is proportional to carbon dioxide irrespective of drift of the carbon dioxide transducer (see text).

The signal U/U_I will only be influenced by carbon dioxide molecules in the pathway of radiation within the sensor head. The length of this pathway is the only critical factor, and this can be well controlled at manufacture. After the divider the signal level is high and the electronics operate under optimal conditions at which drift of amplification or base-line is negligible. The features described explain why the equipment does not need any zero adjustment or recalibration: there are no exterior controls for such procedures. The signal U/U_I is a strict, nearly logarithmic function of expired carbon dioxide concentration. After further processing, mainly linearization, a signal proportional to carbon dioxide concentration is obtained (1 V = 1% carbon dioxide). Apart from the chopping there is no delay in the analysis. One hundred per cent response to a change of carbon dioxide is obtained within 6 ms.

Interference with other gases such as water vapour and nitrous oxide is avoided by the use of a very narrow band-width of infra-red radiation, carefully selected for optimum separation. A contributory factor is that the CO_2 Analyzer measures differences between expired and inspired gases. However, even during induction of nitrous oxide anaesthesia when there are great differences between inspired and expired nitrous oxide (measured with a mass spectrometer), the carbon dioxide signal remains unaffected. When carbon dioxide is added to the inspired gas the Analyzer measures the increase of carbon dioxide over that concentration. Added carbon dioxide should be delivered in a way that ensures that the inspired carbon dioxide concentration, serving as a new baseline, is stable. If this is achieved, then the values for carbon dioxide production are still valid, and the stated end-tidal carbon dioxide becomes the excess

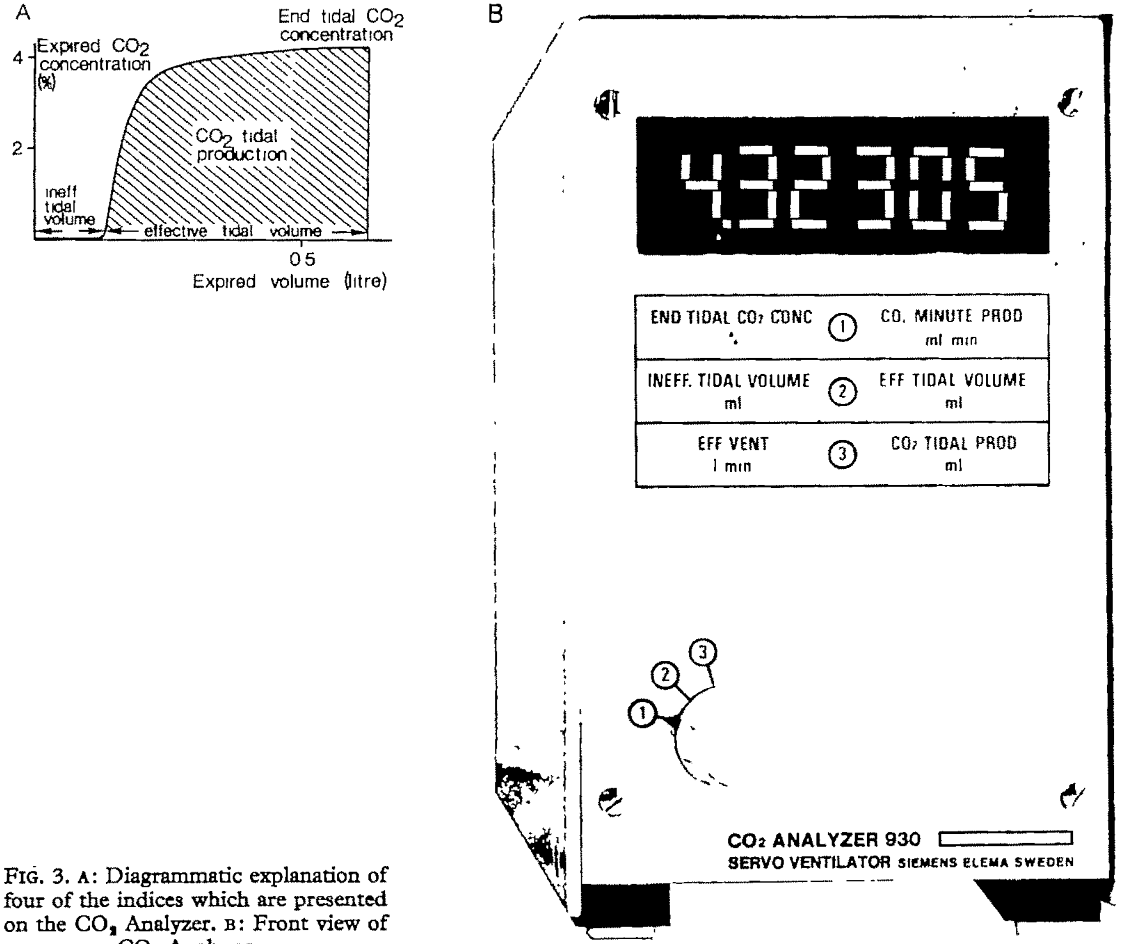


FIG. 3. A: Diagrammatic explanation of four of the indices which are presented on the CO_2 Analyzer. B: Front view of CO_2 Analyzer.

over the inspired value. If the inspired carbon dioxide concentration varies, the Analyzer can give misleading results.

Pressure dependence. With a given gas in the sensor head an increase of pressure will cause an increasing carbon dioxide signal for two reasons. First, the number of carbon dioxide molecules increases in proportion to pressure—a 1% increase causes a 1% increase of the number of radiation-absorbing carbon dioxide molecules. Second, intermolecular forces that increase with pressure will enhance absorption by carbon dioxide. This factor will cause an additional increase of the carbon dioxide signal by 0.8%. In all, a 1% increase of pressure in the sensor head will increase the signal by 1.8%. If the CO_2 Analyzer is calibrated at a barometric pressure of 100 kPa (750 mm Hg) and tested with 4% carbon dioxide at 101 kPa (758 mm Hg) a reading of $4 \times 1.018 = 4.07$ will be obtained. As the concentration is 4% an error of 0.07% will appear if the reading is regarded as concentration. In conjunction with estimates of arterial blood-gas tensions, it is preferable to regard the reading as P_{CO_2} (kPa) and not per cent carbon dioxide as stated on the Analyzer. In this case the true value at a barometric pressure of 101 kPa (758 mm Hg) is 4.04 kPa (40 mm Hg), and the error of the reading is only 0.03 kPa (0.2 mm Hg). In studies in which precision is needed, correction for variations in barometric pressure may be useful. A similar correction should then also be made when very great expiratory airway pressures are applied. In routine clinical use corrections appear to be unnecessary.

Presentation of data. The carbon dioxide signal is processed with the expiratory flow signal to provide further digital and analog information. Figure 3B shows the front panel of the instrument from which six values can be read, four of which are explained in figure 3A.

End-tidal carbon dioxide concentration. The initial carbon dioxide-free part of the expired tidal volume represents gas compressed in the ventilator tubing and humidifier, and gas from conducting airways (*ineffective tidal volume*); the carbon dioxide-containing part is the *effective tidal volume.* As soon as the carbon dioxide concentration exceeds 5% of the previous end-tidal carbon dioxide, the effective part of the tidal volume is recognized. (Ineffective tidal volume is therefore less than the anatomical deadspace.) Averaging of this volume provides a measure of *effective minute ventilation.* Integration of the product carbon dioxide concentration × instantaneous expiratory flow yields the *carbon dioxide tidal production* which is also averaged to *carbon dioxide minute production.* A more appropriate label on the carbon

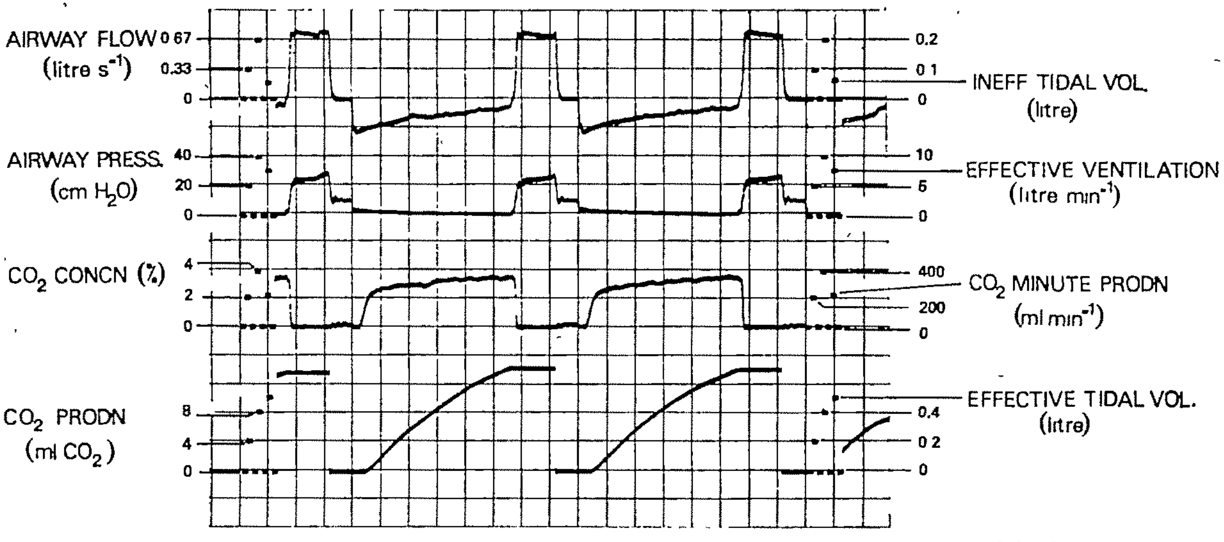


FIG. 4. Mingograf tracing obtained from CO_2 Analyzer. The continuous tracings are of the four signals named on the left, and the calibrations are given by the labelled dots. The values named on the right can be obtained from the penultimate (labelled) dot in the calibration complex which also serves as a scale for these values. For instance, on the uppermost tracing the dots give the calibrations for both the continuous tracing (airway flow) and for ineffective tidal volume. Inspiratory flow is 0.7 litre s^{-1} and ineffective volume 0.06 litre.

dioxide unit would be carbon dioxide elimination which is equal to the carbon dioxide production in the tissues only at steady state.

A simple testing device is available for checking calibration of the carbon dioxide signal against a gas mixture of known carbon dioxide concentration.

Figure 4 shows a tracing from the CO_2 Analyzer recorded on a multi-channel recorder (Mingograf 61, Siemens–Elema AB). Airway pressure, flow rate, carbon dioxide concentration and tidal expired carbon dioxide volume are shown. Every 10 s the recording is interrupted by an automated procedure that prints calibrated scales on each channel. The end-tidal carbon dioxide and $\dot{V}_{CO_2}$ can be read directly. Immediately after the three dots of each scale a fourth dot represents one of the other four data available.

The single breath test for carbon dioxide and determination of V_D/V_T

Although the above method of obtaining carbon dioxide tracings is convenient for clinical use, more information can be obtained from the single breath test for carbon dioxide (SBT-CO_2) in which the x-axis represents volume instead of time. Analog signals available from the Analyzer make it possible to present SBT-CO_2 on an XY oscilloscope or recorder, directly or via a computer, in one of two ways. In the standard presentation (Comroe, 1962), carbon dioxide concentration is recorded against expired volume (fig. 3A). In the presentation suggested by Langley and others (1975), expired carbon dioxide volume is recorded against expired volume. (A separate cable, in which the signals are not interrupted by calibration dots as in figure 4, is used for this purpose.)

With the latter presentation, mixed expired carbon dioxide fraction or partial pressure ($P\bar{E}_{CO_2}$) can be calculated by dividing the volume of carbon dioxide per breath by the tidal volume. V_D/V_T can therefore be calculated if Pa_{CO_2} is measured simultaneously, by substituting in the Bohr equation (Bohr, 1891):

$$V_D/V_T = 1 - \frac{P\bar{E}_{CO_2}}{Pa_{CO_2}}$$

$P\bar{E}_{CO_2}$ can also be calculated from the digital displays during controlled ventilation, by dividing "carbon dioxide tidal production" by the tidal volume—ineffective plus effective tidal volume. This method is unreliable during spontaneous breathing since tidal volume and carbon dioxide tidal production are obtained at different positions of the control knob on the Analyzer and therefore cannot be obtained for the same breath.

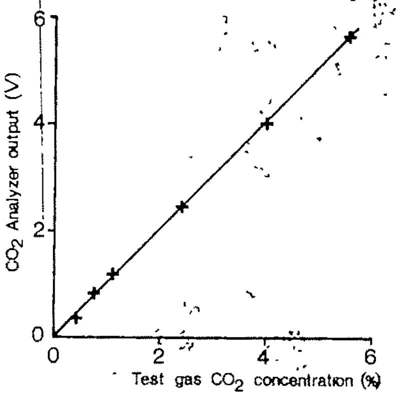


FIG. 5. Output of CO_2 Analyzer (volts) plotted against standard test gas mixtures.

CLINICAL TESTS

The linearity of the CO_2 Analyzer was checked repeatedly with gases analysed with the Scholander apparatus (Scholander, 1947). Figure 5 shows a typical result.

End-tidal carbon dioxide concentration (%) from the infrared Analyzer (IR) and a Perkin Elmer mass spectrometer MGA 1300 A (MS) were compared in anaesthetized patients. The mass numbers used were 12 and 44 for nitrous oxide–oxygen and oxygen–air mixtures respectively. With oxygen–air mixtures (78 observations on 18 individuals) we found: end-tidal carbon dioxide (%) (IR) = 0.218 + 0.927 × end-tidal carbon dioxide (MS) (r = 0.987, SD = 0.22 (residual SD about the regression), SEM of intercept = 0.119, SEM of slope = 0.028).

In oxygen–nitrous oxide mixtures (91 observations on 22 individuals): end-tidal carbon dioxide (%) (IR) = 0.156 + 0.9783 × end-tidal carbon dioxide(MS) (r = 0.987, SD = 0.15, SEM of intercept = 0.068, SEM of slope = 0.017).

A t test showed that the differences in intercept and slope between oxygen–air and oxygen–nitrous oxide mixtures were not significant ($P > 0.05$).

Carbon dioxide production ($\dot{V}_{CO_2}$) (ml min^{-1}) obtained digitally from the CO_2 Analyzer was compared with values obtained from mass spectrometry by multiplying mixed expired carbon dioxide concentration with expired gas volume as measured by the Servo ventilator. Mixed expired gas was obtained by leading the expired gases to a mixing chamber before admission to the mass spectrometer.

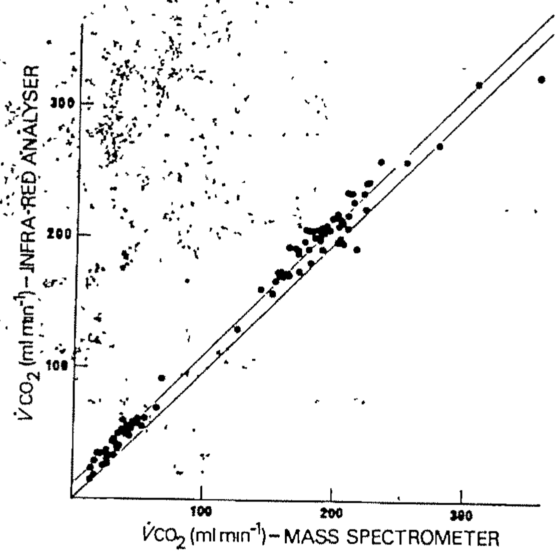


FIG. 6. Comparison of CO_2 Analyzer with mass spectrometer. Nitrous oxide–oxygen mixture.

For oxygen–air mixtures (73 observations on 18 individuals): $\dot{V}_{CO_2}$ (IR) = $-0.649+1.047\times\dot{V}_{CO_2}$ (MS) ($r = 0.991$, SD = 14.0, SEM of intercept = 2.84, SEM of slope = 0.0147).

For oxygen–nitrous oxide mixtures (91 observations on 22 individuals) (fig. 6): $\dot{V}_{CO_2}$ (IR) = $10.56+1.006\times\dot{V}_{CO_2}$ (MS) ($r = 0.993$, SD = 10.1, SEM of intercept = 2.728, SEM of slope = 0.0174).

A t test showed that the difference in slope between oxygen–air and oxygen–nitrous oxide mixtures was not significant ($P > 0.05$). The difference in the intercepts was significant ($0.01 > P > 0.005$).

The physiological deadspace: tidal volume ratio was measured during spontaneous breathing by the single breath method. At steady state, mixed expired gas was collected for analysis (Scholander, 1947), arterial blood was sampled and the single breath profile was recorded. The mixed expired carbon dioxide fraction was obtained from a single tidal breath. In 10 patients with lung disease the following regression was obtained: V_D/V_T (SBT-CO_2) = $0.028+0.8599\times V_D/V_T$ (Scholander) ($r = 0.949$, SD = 0.024, SEM of intercept = 0.041, SEM of slope = 0.106).

DISCUSSION

The operating theatre or intensive care unit make special demands on technical equipment with respect to size, maintenance and safety. The CO_2 Analyzer is compact and silent and has only one cable running with the ventilator tubing. The analysis of carbon dioxide within the airway is instant and makes a gas withdrawal system unnecessary. This makes the device simple to use, and safety is not compromised by the potential for creating a subatmospheric pressure in the airway.

The features that eliminate the need for daily calibration were described in some detail to illustrate how simple principles can be realized by modern electronics. The price of achieving this simplicity is limited usefulness in systems with carbon dioxide in the inspired gas, and that the Analyzer can only be used in conjunction with the Servo 900 ventilator.

The results show that the measurement of $\dot{V}_{CO_2}$ and end-tidal carbon dioxide is sufficiently accurate for research purposes.

The carbon dioxide measurement was not affected by nitrous oxide. The signal representing $\dot{V}_{CO_2}$ showed similar results in adults with and without nitrous oxide. The significant difference in intercept should not be regarded as implying that the CO_2 Analyzer yields a positive carbon dioxide reading at zero $\dot{V}_{CO_2}$ values. Thus the relationship between the two $\dot{V}_{CO_2}$ estimates is non-linear and is not adequately described by the regression equation. It is, however, difficult to see why non-linearity should be confined to the nitrous oxide–oxygen mixture. In the presence of nitrous oxide, the mass spectrometer was used in the anaesthetic mode, which made the accuracy of carbon dioxide determination less, but did not introduce a systematic error. The difference in the intercepts should not be overemphasized, for in view of the complexity of both methods the extent of the agreement was reassuring.

Estimation of V_D/V_T during spontaneous breathing is acceptable for clinical use.

Greater accuracy for V_D/V_T would be expected during controlled ventilation, because of the smaller breath-to-breath variation in tidal volume and carbon dioxide content. Apart from Pa_{CO_2} all the data needed for calculation of V_D/V_T can be obtained from the carbon dioxide unit itself. For example, mixed expired carbon dioxide concentration can be obtained from either $\dot{V}_{CO_2}/\dot{V}_E$ or from carbon dioxide tidal production/(ineffective + effective tidal volume).

The most common application of the analysis of expired carbon dioxide is control of ventilation to maintain suitable end-tidal and arterial P_{CO_2} values (Collier, 1955; Dahlgren and Symreng, 1974; Prakash et al., 1978). However, although useful under most circumstances, the use of end-tidal carbon dioxide has limitations in the presence of lung disease

(Fletcher and Jonson, 1977). The present CO_2 Analyzer yields information that can reveal subclinical lung disease (see below), and we are studying how this information can be used to improve the usefulness, and to avoid the pitfalls, of end-tidal measurements in the control of ventilation.

A rough guide to ventilatory needs may be obtained from a nomogram (Radford, 1955; Engström and Herzog, 1959; Engström et al., 1962). However, our experience with the CO_2 Analyzer suggests that large variations in $\dot{V}_{CO_2}$ and, to a lesser extent, V_D/V_T, are commonplace during surgery.

When a standard ventilator setting does not give an acceptable Pa_{CO_2}, the information from the CO_2 Analyzer should be used in a logical search for the reason. The carbon dioxide production may be chosen as the starting point. If, at steady state, this is greater than expected, the need for ventilation is correspondingly increased. Further search should be directed towards non-pulmonary factors, such as fever, pain, anxiety and shivering.

In other cases the alveolar ventilation is low. In the presence of normal or high total ventilation this implies increased deadspace. Total "physiological" deadspace ventilation can be calculated and the physiological deadspace (ml) by division with the frequency. Increased V_D can result from a high ineffective ventilation (absolute deadspace) (Bartels et al., 1954). Increased compressed volumes in the tubings or humidifier may be caused by increased airway pressures or inadequate levels of water in some humidifiers. This problem is of course of importance in children and especially in infants (Okmian, 1963). The lung mechanics calculator 940 (Jonson et al., 1975) (Siemens–Elema AB) gives additional information about compliance and resistance, possible causes of an increased airway pressure.

If the reason for dysfunction is still not obvious, increased intrapulmonary or alveolar deadspace must be present. This can be caused by several factors: ventilation–perfusion mismatching, pulmonary embolism and venous admixture may all contribute. The CO_2 Analyzer offers some possibilities for further analysis. Sequential emptying of lung compartments with different ventilation–perfusion relationships yields SBT-CO_2 with a poorly defined, steeply sloping alveolar plateau (fig. 7, left). This may be found in obstructive lung disease, even when other signs are missing.

Non-sequential phenomena, such as venous admixture or synchronous emptying of lung compartments with different carbon dioxide contents, yield another pattern (fig. 7, right). This pattern has been observed in conjunction with hypovolaemia and pulmonary embolism (non-perfusion of lung compartments) and congenital heart disease with variable right to left shunts (Prakash et al., 1978).

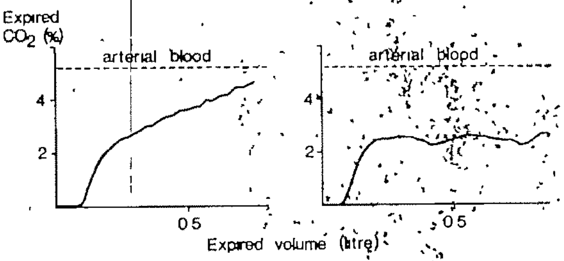


FIG. 7. Left: carbon dioxide single breath test from a 73-yr-old man with emphysema. Note the steeply sloping, poorly defined alveolar plateau. This is caused by sequential emptying of lung compartments with greatly differing carbon dioxide concentrations. The arterial–end-tidal difference is indicative of alveolar deadspace. Right: carbon dioxide single breath test from a 72-yr-old man with massive pulmonary emboli. The alveolar plateau is clearly defined and shows marked cardiogenic oscillations. The simultaneous emptying of well-perfused and under-perfused lung compartments causes a large alveolar deadspace and a large arterial–end-tidal carbon dioxide difference. The horizontal plateau suggests the absence of pre-existing obstructive lung disease.

The usefulness and limitations of SBT-CO_2 as a diagnostic tool in lung disease remain to be explored.

Monitoring of the electrocardiogram (e.c.g.) and ventilation may continue undisturbed in spite of even circulatory arrest. As gas exchange is the immediate vital function of both ventilation and circulation, monitoring of carbon dioxide elimination or oxygen uptake offers a more fundamental guarantee against unobserved life-threatening malfunction of vital organs. Any sudden severe malfunction depresses the carbon dioxide elimination via the lungs (Smalhout and Kalenda, 1975). Such an observation should lead to a systematic search for the reason, starting with control of ventilation and the e.c.g. A common cause for circulatory depression during thoracic surgery in the presence of undisturbed e.c.g. and ventilation is temporary interference with venous return. It is important to be able to recognize such events before, for example, hypoxic arrhythmias occur. Continuous monitoring of aerobic metabolism probably offers the best prospects of early discovery of malignant hyperthermia.

Apart from ventilating the lungs in response to end-tidal P_{CO_2}, the control of other routine procedures may be based on information from gas analysis. Profound hypothermia during anaesthesia for cardiac surgery in infants may be performed with guidance from carbon dioxide analysis (Prakash et al., 1978). At extubation of the trachea it has been found useful to check the ability to maintain adequate gas exchange during a spontaneous ventilation test (Prakash et al., 1977). The efficiency of ventilation is, in some patients, dependent upon the breathing pattern produced by the ventilator; this aspect of the use of instant analysis of the gas exchange is largely unexplored.

Note added in proof: New evidence indicates that the balance of gases influences the reading of the CO_2 Analyzer (A. v. Bijnen, Department of Hospital Engineering, University Hospital, Leyden, The Netherlands, personal communication). Nitrous oxide should cause increased, and oxygen decreased readings. A 65% nitrous oxide:35% oxygen mixture should result in carbon dioxide values that are slightly too great. Although the comparison between different mixtures of gases presented in the article does not show significant differences in slopes, a trend towards higher readings in the presence of nitrous oxide can be observed. The error is not related to absorbtion of infra-red radiation of nitrous oxide, but rather to intermolecular interaction between gases. Its nature and magnitude require further studies.

ACKNOWLEDGEMENTS

This study was supported by the Swedish Medical Research Council, grant 14X–02872 and by the Swedish National Association against Chest and Heart Diseases.

REFERENCES

Bartels, J., Severinghaus, J. W., Forster, R. E., Briscoe, W. A., and Bates, D. V. (1954). The respiratory dead space measured by single breath analysis of oxygen, carbon dioxide, nitrogen or helium. *J. Clin. Invest.*, **33**, 41.

Bohr, C. (1891). Ueber die Lungenathmung. *Skand. Arhiv. Physiol.*, **2**, 236.

Collier, C. R. (1955). Continuous rapid infrared CO_2 analysis. *J. Lab. Clin. Med.*, **45**, 526.

Comroe, J. H. (1962). *The Lung*, 2nd edn, p. 107. Chicago: Year Book Medical Publishers.

Dahlgren, B. E., and Symreng, T. (1974). Instant control of the alveolar P_{CO_2} in neurosurgical operations by the use of Godart–Statham capnograph. *Opusc. Med.*, **19**, 271.

Engström, C.-G., and Herzog, P. (1959). Ventilation nomogram for practical use with the Engstrom respirator. *Acta Chir. Scand.* (Suppl.), 245, 37.

—— —— Norlander, O. P., and Swensson, S. A. (1962). Ventilation nomogram for the newborn and small children to be used with the Engstrom respirator. *Acta Anaesthesiol. Scand.*, **6**, 175.

Fletcher, R., and Jonson, B. (1977). Skattning av arteriellt P_{CO_2} genom matning av CO_2 i expirationsluft. *Sven. Läkaresallsk. Riksstdm.*, p. 84. Stockholm: Hygiea.

Galdston, M., Benjamin, B., and Hurewitz, M. (1951). "Alveolar air" and arterial blood-gas tension studies in normal and chronic lung disease patients. *Fed. Proc.*, **10**, 47.

Ingelstedt, S., Jonson, B., Nordström, L., and Olsson, S.-G. (1972). A servo-controlled ventilator measuring expired minute volume, airway flow and pressure. *Acta Anaesthesiol. Scand.* (Suppl.), **47**, 7.

Jonson, B., Nordström, L., Olsson, S.-G., and Åkerback, D. (1975). Monitoring of ventilation and lung mechanics during automatic ventilation. A new device. *Bull. Physiopathol. Respir.*, **11**, 729.

Langley, F., Even, P., Duroux, P., Nicolas, R. L., and Cumming, G. (1975). Ventilatory consequences of unilateral pulmonary artery occlusion. *Colloques Instit. Nat. Santé Rech. Méd.*, **51**, 209.

Okmian, L. G. (1963). Artificial ventilation by respirator for newborn infants during anaesthesia. *Acta Anaesthesiol. Scand.*, **7**, 31.

Prakash, O., Jonson, B., Bos, E., Meij, S., Hugenholtz, P. G., and Hekman, W. (1978). Cardiorespiratory and metabolic effects of profound hypothermia. *Crit. Care Med.*, **6**, 340.

—— —— Meij, S., Bos, E., Hugenholtz, P. G., Nauta, J., and Hekman, W. (1977). Criteria for early extubation after intracardiac surgery in adults. *Anesth. Analg. (Cleve.)*, **56**, 703.

Radford, E. P. (1955). Ventilation standards for use in artificial respiration. *J. Appl. Physiol.*, **7**, 451.

Scholander, P. F. (1947). Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. *J. Biol. Chem.*, **167**, 235.

Smalhout, B., and Kalenda, Z. (1975). *An Atlas of Capnography*, p. 28. Zeist: Kerckebosch.

ETUDES CLINIQUES SUR L'ECHANGE DE GAZ PENDANT L'USAGE D'UN SYSTEME VENTILATOIRE D'APPOINT—METHODE BASEE SUR L'ANALYSEUR DE CO_2 SIEMENS-ELEMA (SIEMENS-ELEMA CO_2 ANALYZER)

RESUME

Nous décrivons dans cet article un nouvel analyseur portatif à infrarouges que l'on utilise avec le Servoventilateur Siemens-Elema. La tête du système sensible est en forme d'Y; elle relie le patient au tuyau du ventilateur et permet de déterminer instantanément la quantité de gaz carbonique. Cet appareil est basé sur des principes simples qui peuvent être réalisés grâce aux techniques modernes. Il permet par exemple d'éviter toute interférence de la part des gaz anesthésiants et élimine la nécessité de procéder à des étalonnages. Toute concentration de gaz carbonique inspiré, d'une valeur autre que zéro, gêne les mesures. L'intégration du signal gaz carbonique dans le signal du débit émanant du Servoventilateur permet d'obtenir des données sur l'excrétion de gaz carbonique, et en faisant quelques calculs complémentaires on peut obtenir la V_D/V_T, lorsqu'on connaît la Pa_{CO_2}. On a trouvé que la précision de la détermination du gaz carbonique en fin d'expiration ainsi que celle de l'élimination du gaz carbonique étaient adéquates pour les

besoins de la recherche, et qu'il en était de même pour la V_D/V_T du point de vue clinique. Cet appareil est considéré comme ayant son utilité dans les salles d'opérations et les salles de soins intensifs, pour la surveillance générale, pour la détermination des impératifs ventilatoires, et pour faire des recherches sur l'importance et les causes de l'augmentation de l'espace mort.

KLINISCHE STUDIEN DES GASAUSTAUSCHES BEI KÜNSTLICHER BELÜFTUNG—EINE METHODE MIT VERWENDUNG DES SIEMENS-ELEMA CO_2 ANALYZER

ZUSAMMENFASSUNG

Wir beschreiben einen neuen, transportablen Infrarot-Analysator zur Benutzung mit dem Siemens–Elema–Servoventilator. Der Sensorkopf stellt ein Y-formiges Stuck dar, das den Patienten an den Ventilator anschliesst, und sofortige Kohlendioxydbestimmung ermöglicht. Es beruht auf einfachen Prinzipien, die durch moderne Methoden realisiert werden konnen, und bietet z.B. Freiheit von Störung durch Anästhesiegase, und eliminiert die Notwendigkeit einer Kalibrierung. Ein Vorhandensein von angesaugten Kohlendioxydkonzentrationen beeinträchtigt die Messungen. Integrierung des CO_2-Signals mit dem Durchflusssignal vom Servoventilator ergibt Daten uber CO_2-Ausscheidung, und zusätzliche Berechnungen ergeben V_D/V_T, wenn Pa_{CO_2} bekannt ist. Die Genauigkeit der Endausatmung von Kohlendioxyd und von dessen Ausscheidung hat sich als ausreichend fur Forschungszwecke erwiesen, und die Genauigkeit von V_D/V_T für klinische Zwecke. Das Gerät ist wertvoll in Operationssaal und Intensivstation—für Überwachung, für eine Richtlinie der Beluftungserfordernisse und für die Untersuchung von Grösse und Ursachen vergrösserten Totraums.

ESTUDIOS CLINICOS DEL INTERCAMBIO DE GASES DURANTE APOYO VENTILATORIO—UN METODO EN QUE SE USA UN SIEMENS–ELEMA CO_2 ANALYZER

SUMARIO

Describemos un nuevo analizador infra-rojo portátil para uso con el ventilador Siemens–Elema. La cabeza detectora constituye una pieza en Y que conecta al paciente con la tubería del ventilador y arroja una determinación instantánea del dióxido de carbono. Se basa en principios sencillos que se pueden poner en práctica con técnicas modernas que ofrecen por ejemplo una independencia con respecto a los gases anestéticos y eliminan la necesidad de calibración. Una concentración de dióxido de carbono inspirado sin cero interfiere con las mediciones. La integración de la señal de dióxido de carbono con la señal del flujo del Servo-ventilador arroja datos sobre la excreción de dióxido de carbono y un cálculo adicional suministra el V_D/V_T si se conoce el Pa_{CO_2}. La exactitud de la determinación del dióxido de carbono respiratorio-terminal y de la eliminación del dióxido de carbono se consideró adecuada con respecto a los fines de la investigación y la del V_D/V_T para fines clínicos. Se considera que el aparato es valioso en la sala de operación y en el servicio de cuidados intensivos, para el control así como para guía respecto de las necesidades ventilatorias, al igual que para la investigación de la magnitud y de las causas del creciente espacio muerto.

Br. J. Anaesth. (1980), **52**, 501

COMPARATIVE EFFECTS OF CALCIUM CHLORIDE AND CALCIUM GLUCEPTATE

L. J. Drop and D. J. Cullen

SUMMARY

Calcium chloride and calcium gluceptate were compared in their ability to increase plasma ionized calcium concentrations ([Ca^{2+}]). To correct a low ionized calcium concentration, each of 10 critically ill patients received both calcium chloride (10 ml of a 10% solution, containing elemental calcium 27 mg ml^{-1}) and calcium gluceptate (20 ml, containing elemental calcium 18 mg ml^{-1}) over a 5-min period in randomized order approximately 6 h apart. [Ca^{2+}] and haemodynamic variables (mean arterial pressure (MAP), mean right atrial pressure (RAP) and heart rate (HR)) were monitored for a 30-min period following completion of calcium infusion. Infusion of either calcium preparation was associated with similar increases in [Ca^{2+}] (5 min after infusion of calcium chloride: 33 ± 3.1%; calcium gluceptate: 32 ± 4.3% (mean ± SEM)) and the effects on MAP were similar for each solution (11.1 ± 1.8% and 9.7 ± 2.4%, respectively).

Calcium preparations may be infused i.v. during anaesthesia or in the critical care unit (Drop and Laver, 1975; Taylor et al., 1978). However, we do not know the effect on plasma ionized calcium concentration ([Ca^{2+}]) following either i.v. calcium chloride or calcium gluceptate administration. These two commonly used preparations differ in their elemental calcium content (calcium chloride: 27 mg ml^{-1}; calcium gluceptate: 18 mg ml^{-1}) and in the availability of the calcium ion. Calcium chloride is completely dissociated in solution and calcium is present in the free, ionized form. In calcium gluceptate, not all of the calcium is in free ionized form because a complex with the gluceptate radical is formed.

We have compared changes in [Ca^{2+}] and in haemodynamic variables following i.v. administration of 10% calcium chloride 10 ml and calcium gluceptate 20 ml in patients in whom initial [Ca^{2+}] values were substantially less than normal.

PATIENTS AND METHODS

Ten patients who required artificial ventilation of the lungs following major abdominal or vascular surgery were studied. The age range was 27–90 yr, body weight 48.6–76.9 kg. In each patient, surgery had been completed at least 12 h before the time of study; no blood or blood products had been administered in the preceding 4-h period. In view of the potentially serious complications that may arise following calcium infusion in patients with abnormalities in potassium balance (Surawicz, 1967a) or those receiving digitalis (Eliot and Blount, 1961), such patients were excluded from the study.

During the study period, i.v. fluids were restricted to 25 ml h^{-1}. Haemodynamic measurements were obtained at zero airway pressure. Intra-arterial and right atrial pressures were recorded as part of routine monitoring employed in these patients from appropriate indwelling catheters via Statham P23 AA transducers. Mean pressures were determined by electronic integration. Lead II of the e.c.g. was recorded at a paper speed of 25 mm s^{-1} to determine heart rate (HR).

Plasma ionized calcium concentration ([Ca^{2+}]) was measured with a calcium-selective electrode system, calibrated before and after passage of each plasma sample with aqueous solutions of known [Ca^{2+}] (Drop and Laver, 1975). Arterial P_{O_2}, P_{CO_2} and pH were measured with standard commercial electrodes at 37 °C and corrected for body temperature when required. Total calcium concentration ([Ca]), sodium (Na^+), potassium (K^+), inorganic phosphorus (P_i) and total protein (TP) concentrations were determined by standard methods.

Immediately before infusion of calcium because of hypocalcaemia, an arterial sample was obtained for

---

Lambertus J. Drop, M.D., Ph.D.; David J. Cullen, M.D.; Anesthesia Services of the Massachusetts General Hospital and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts 02114, U.S.A.

Correspondence to L. J. D., Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts 02114, U.S.A.

0007–0912/80/050501–05 $01.00

© Macmillan Journals Ltd 1980

determination of biochemical variables. In all patients, P_{O_2} ranged from 10.67 to 34.67 kPa, P_{CO_2} from 4.27 to 6.13 kPa, pH from 7.35 to 7.49; Na^+ from 132 to 145 mmol·litre^{-1}; K^+ from 3.9 to 4.9 mmol litre^{-1} and total protein from 46 to 57 g litre^{-1}. These values were known for each patient before each calcium infusion. Sinus rhythm was present in each patient, and heart rate ranged from 68 to 108 beat min^{-1}.

Each patient received infusions of both calcium chloride (10 ml of a 10% solution, containing elemental calcium 27 mg ml^{-1}) (Goodman and Gilman, 1970) and calcium gluceptate (20 ml, containing elemental calcium 18 mg ml^{-1} as specified on the label) over a 5-min period in randomized order approximately 6 h apart. Heparinized arterial blood specimens were withdrawn and haemodynamic measurements made immediately before the calcium infusion and 5, 10, 20 and 30 min following completion of the calcium infusion.

Student's *t* test was used to test for statistical significance; values are given as mean ± SEM.

RESULTS

Details of the patients are in table I. Mean initial [Ca^{2+}] before each calcium infusion was less than normal (1.12 ± 0.03 mmol litre^{-1}) (Drop et al., 1978) and less than predicted by the McLean–Hastings nomogram (McLean and Hastings, 1935) (fig. 1). Calcium infusion resulted in a sustained increase in [Ca^{2+}] (table II) and in mean arterial pressure (table III); changes in these variables were not materially influenced by the choice of calcium preparation. No significant changes were recorded in mean right atrial pressure, heart rate or cardiac rhythm. For the same increase in [Ca^{2+}], [Ca] increased more following calcium gluceptate than after calcium chloride (table II). Other biochemical variables did not change during the periods of observation.

TABLE I. *Ten patients who received calcium infusion for ionized hypocalcaemia*

Age (yr)	Sex	Condition	Operation
82	M	Pelvic abscess, sepsis	Drainage of abscess
68	M	Peripheral obstructive vascular disease	Aorto–femoral graft
27	F	Ulcerative colitis	Subtotal colectomy
61	M	Gastric varices, liver cirrhosis	Partial gastrectomy
63	M	Perforated colon, sepsis	Partial colectomy, small bowel resection
56	M	Small bowel obstruction	Small bowel resection
55	M	Bleeding gastric ulcer	Subtotal gastrectomy, splenectomy
90	F	Subhepatic abscess	Small bowel resection, drainage of abscess
57	M	Bleeding gastric ulcer	Subtotal gastrectomy, splenectomy
60	F	Multiple injury after motor vehicle accident	Abdominal exploration

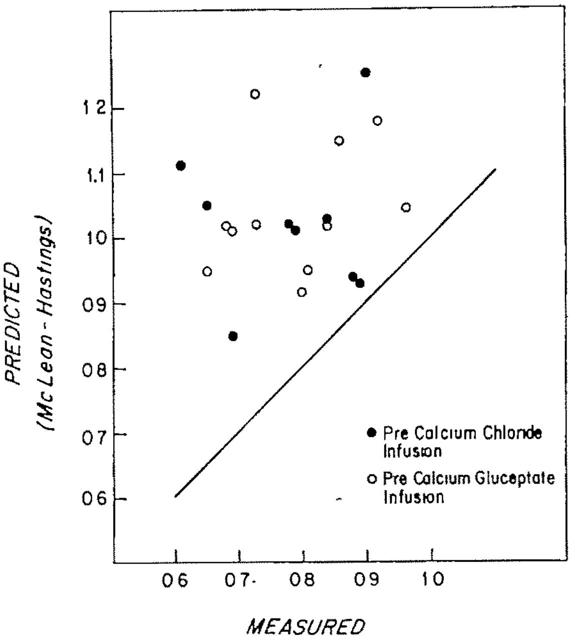


FIG. 1. Ionized calcium values predicted by use of the McLean–Hastings nomogram plotted against those directly measured by electrode in 10 critically ill patients before infusion of either calcium solution. The solid line represents the line of perfect agreement. All data points are positioned to the left of this line, that is measured [Ca^{2+}] values were smaller than predicted. To predict [Ca^{2+}] by use of the McLean–Hastings nomogram, two variables are known (total calcium and total protein); other values are assumed to be as follows: albumin/globulin ratio = 1.8, pH = 7.35 and temperature = 25 °C.

DISCUSSION

In critically ill patients with ionized hypocalcaemia, calcium chloride 10 ml (elemental calcium 27 mg ml^{-1}) is equivalent to calcium gluceptate 20 ml (elemental calcium 18 mg ml^{-1}), both infused i.v. over a 5-min period, in terms of the increase in [Ca^{2+}]. The changes in haemodynamic variables associated with infusion of these amounts of calcium were also similar.

TABLE II. *Effects of calcium solutions on indices of calcium homeostasis (mean ± SEM).* *** $P < 0.001$; ** $P < 0.01$. $[Ca^{2+}]$ = *ionized calcium;* $[Ca]$ = *total calcium;* P_i = *inorganic phosphorous concentrations (mmol litre*$^{-1}$*)*

		Time after end of infusion (min)				
		Control	5	10	20	30
Calcium chloride (10 ml in 5 min)	$[Ca^{2+}]$	0.79 ± 0.04	1.06 ± 0.05***	1.00 ± 0.05***	0.98 ± 0.04***	0.91 ± 0.04***
	$[Ca]$	2.08 ± 0.10	2.44 ± 0.11***	2.43 ± 0.14***	2.39 ± 0.12***	2.27 ± 0.13**
	P_i	0.57 ± 0.13	0.57 ± 0.13	0.66 ± 0.13	0.66 ± 0.13	0.67 ± 0.13
Calcium gluceptate (20 ml in 5 min)	$[Ca^{2+}]$	0.79 ± 0.04	1.04 ± 0.05***	1.00 ± 0.05***	0.95 ± 0.04***	0.91 ± 0.04***
	$[Ca]$	2.08 ± 0.05	2.71 ± 0.14***	2.57 ± 0.11***	2.51 ± 0.10***	2.43 ± 0.07***
	P_i	0.66 ± 0.15	0.62 ± 0.13	0.62 ± 0.16	0.69 ± 0.16	0.71 ± 0.16

TABLE III. *Effects of calcium infusion on haemodynamic variables (mean ± SEM).* *$P < 0.05$; †$P < 0.025$; **$P < 0.01$; ***$P < 0.001$. *MAP = mean arterial pressure; RAP = mean right atrial pressure; HR = heart rate*

			Time after end of infusion (min)			
		Control	5	10	20	30
Calcium chloride (10 ml in 5 min)	MAP (mm Hg)	79.1 ± 8.3	88.1 ± 8.3†	86.3 ± 8.3***	84.6 ± 8.8*	84.0 ± 8.5*
	RAP (mm Hg)	9.8 ± 10	8.5 ± 1.0	9.0 ± 1.1	8.8 ± 0.9	9.0 ± 0.9
	HR (beat min^{-1})	94.0 ± 3.6	95.0 ± 4.1	96.0 ± 3.7	98.0 ± 3.9	95.0 ± 3.6
Calcium gluceptate (20 ml in 5 min)	MAP (mm Hg)	81.8 ± 7.5	89.7 ± 9.7†	85.0 ± 7.9**	84.0 ± 8.1*	83.5 ± 9.4
	RAP (mm Hg)	7.2 ± 0.7	8.3 ± 0.8	8.2 ± 0.8	8.1 ± 1.3	8.3 ± 1.2
	HR (beat min^{-1})	96.0 ± 3.5	97.0 ± 2.8	94.0 ± 4.4	97.0 ± 4.2	93.0 ± 4.5

We did not observe cardiac arrhythmia during or following calcium infusion.

The calcium-selective electrode system enabled detection of initial ionized hypocalcaemia in our patients, present before calcium infusion. Such detection would have been impossible with the McLean–Hastings nomogram (fig. 1), the traditional method for estimating $[Ca^{2+}]$. In the nomogram, two known variables (total calcium and total protein concentrations) are used to predict calcium ion concentration. All our directly measured data points were positioned to the left of the line of perfect agreement, indicating that hypocalcaemia was not apparent from total calcium measurement. This observation has been made previously (Drop and Laver, 1975; Drop and Scheidegger, 1979).

We had compared the increase in $[Ca^{2+}]$ following addition of different amounts of calcium gluceptate or calcium chloride to aliquots of heparinized blood drawn from a normal volunteer. Such an empirical approach appeared necessary since the elemental calcium content of a calcium solution does not provide information on its calcium ion concentration nor does it predict $[Ca^{2+}]$ increase in patients following its infusion i.v. Calcium chloride is completely dissociated in solution and calcium is present in the free, ionized form. In calcium gluceptate solution, calcium is present both in the free ionized form and and as the calcium gluceptate complex. Measurement of $[Ca^{2+}]$ in the tested solutions is unhelpful since calcium ion concentration is substantially greater than the useful sensitivity range of the calcium electrode system. In addition, the pH of these solutions is unstable so that the electrode may respond, not exclusively to calcium ion activity, but to that of hydrogen ion also. Following i.v. calcium infusion, some calcium will remain in the free, ionized form and some is bound by protein and complexed to different naturally occurring anions. In the case of calcium gluceptate infusion, there is initial binding of the calcium ion by the gluceptate radical also. Thus, direct $[Ca^{2+}]$ measurement in blood from patients is essential to evaluate the effectiveness of each calcium preparation in increasing $[Ca^{2+}]$.

The calcium-selective electrode system used in this study represents a practical method for the determination of the physiologically active portion of plasma calcium concentration in small specimens of whole blood. Madsen and Ølgaard (1977) reported that the within-day coefficient of variation for quadruple analyses was 1.8%. Data by these authors and from this laboratory (Drop, Fuchs and Stulz, 1978) have demonstrated a relatively small effect of pH throughout the physiological pH range on [Ca^{2+}] measurement, while the effect of adding small amounts of heparin to the blood sample is minimal. Furthermore, the arterial–venous difference in [Ca^{2+}] is negligible. Recent data (Drop, Fuchs and Stulz, 1978) obtained concurrently in the United States (Boston, Massachusetts) and in Europe (Göttingen, Germany) have shown that [Ca^{2+}] is normally maintained within very narrow limits ([Ca^{2+}] = 1.12 ± 0.02 mmol $litre^{-1}$, mean ± SEM; $n = 100$). In the case of a calibrated calcium-selective electrode system, the results of [Ca^{2+}] determinations are available approximately 3 min following initiation of the analytical procedure. We have found this feature to be of particular value in the documentation and prompt therapy of hypocalcaemic tetany during anaesthesia (Drop and Miller, 1980) and in the experimental setting allowing for study of cardiac (Drop et al., 1978; Stulz et al., 1979) and haemodynamic function (Scheidegger and Drop, 1979) during steady-state abnormalities in calcium ion balance.

In our patients, i.v. infusions of calcium chloride 10 ml and calcium gluceptate 20 ml were followed by similar changes in [Ca^{2+}] and haemodynamic variable; the advantages of one form of calcium over another were not apparent. Since the calcium ion is known to be a major determinant of change in the phase 2 component of the cardiac action potential (Surawicz, 1967b), effective refractory period (Surawicz, 1967a), ventricular excitability (Surawicz, 1967a) and conduction velocity (Goodman and Gilman, 1970), it seems most likely that the safety of calcium infusion depends primarily upon the rate of [Ca^{2+}] changes in blood. In our patients, [Ca^{2+}] was adjusted to normal with calcium administration and a disturbance of cardiac rhythm was not observed. In view of the known influence of plasma potassium concentration (Surawicz, 1967a) and digitalis therapy (Eliot and Blount, 1961) on the development of calcium-induced ventricular arrhythmias, plasma K^+ was ascertained to be in the normal range and patients receiving digitalis therapy were excluded. In addition, available instrumentation permitted the close monitoring of [Ca^{2+}] throughout the observation periods.

Our data indicate that an increase in [Ca^{2+}] was associated with increased MAP (approximately 10% at 5 min) without significant alterations in HR. Increased MAP may occur secondary to increased cardiac output or to increased systemic vascular resistance, or both. Since data on cardiac output or systemic vascular resistance were not available, the mechanism responsible for increased MAP in our patients remains uncertain. However, recent experimental data (Drop and Scheidegger, 1980) have shown that the haemodynamic response to calcium infusion was influenced by the initial [Ca^{2+}] value. When calcium was infused with the initial [Ca^{2+}] values less than normal, increased MAP was recorded principally as a result of increased cardiac output. In contrast, when calcium was infused to increase [Ca^{2+}] from normal, increased peripheral vascular resistance was the principal cause of the increase in MAP.

In this study we tested two calcium solutions available in the United States. Hempelmann and associates (1978) found that the influence of 5.5% calcium gluconate 10 ml on haemodynamic function was less than that of 10% calcium chloride 10 ml in patients subjected to cardiac operations. Although [Ca^{2+}] was not measured by these authors, it is likely that increase in [Ca^{2+}] was less following the calcium gluconate infusion as compared with calcium chloride infusion.

Finally, in our patients, [Ca^{2+}] was adjusted to normal. Caution with excessive use of calcium should be exercised since data are not available to document the benefit or possible disadvantages of [Ca^{2+}] increased to much greater than normal in patients in whom there is evidence of myocardial ischaemia.

ACKNOWLEDGEMENTS

This study was supported in part by NIGMS Grant 15904–07. The authors wish to express their gratitude to Ms Bonnie-Jean Unger for secretarial assistance.

REFERENCES

Drop, L. J., Fuchs, C., and Stulz, P. M. (1978). Determination of blood ionized calcium in a large segment of the normal adult population. *Clin. Chim. Acta*, **89**, 503.

—— Geffin, G. A., O'Keefe, D. D., Chaffin, J. S., and Daggett, W. M. (1978). Left ventricular pump performance during sustained hypo- and hypercalcemia. *Surg. Forum*, **29**, 259.

—— Laver, M. B. (1975). Low plasma ionized calcium and response to calcium therapy in critically ill man. *Anesthesiology*, **43**, 300.

Drop, L. J., and Miller, E. V. (1980). Biochemical alterations during tetany. A case report. *Anesthesiology*, **52**, 82.

—— Scheidegger, D. (1979). Haemodynamic consequences of citrate infusion in the anaesthetized dog: comparison between two citrate solutions and the influence of beta blockade. *Br. J. Anaesth.*, **51**, 513.

—— —— (1980). Plasma ionized calcium concentration: an important determinant of the hemodynamic response to calcium infusion. *J. Thorac. Cardiovasc. Surg.*, **79**, 425.

Eliot, R. S., and Blount, S. G. (1961). Calcium, chelation and digitalis. A clinical study. *Am. Heart J.*, **62**, 7.

Goodman, L. S., and Gilman, A. (1970). *The Pharmacological Basis of Therapeutics*, p. 805. New York: The Macmillan Company.

Hempelmann, G., Piepenbrock, S., Frerk, C., and Schleussner, E. (1978). Beeinflussung von Herz-Kreislauf Parametern durch Calciumglukonat und Calcium-chlorid. *Anaesthesist*, **27**, 516.

McLean, F. C., and Hastings, A. B. (1935). The state of calcium in the fluids of the body. *J. Biol. Chem.*, **108**, 285.

Madsen, S., and Ølgaard, K. (1977). Evaluation of a new automatic calcium ion analyzer. *Clin. Chem.*, **23**, 690.

Scheidegger, D., and Drop, L. J. (1979). The relationship between duration of Q–T interval and plasma ionized calcium concentration: Experiments with acute, steady-state [Ca^{2+}] changes in the dog. *Anesthesiology*, **51**, 143.

Stulz, P. M., Scheidegger, D., Drop, L. J., Lowenstein, E., and Laver, M. B. (1979). Ventricular pump performance during hypocalcemia. *J. Thorac. Cardiovasc. Surg.*, **78**, 185.

Surawicz, B. (1967a). Arrhythmias and electrolyte disturbances. *Bull. N.Y. Acad. Med.*, **43**, 1160.

—— (1967b). Relationship between electrocardiogram and electrolytes. *Am. Heart J.*, **73**, 814.

Taylor, B., Sibbald, W. J., Edmonds, M. W., Holloday, R. L., and Williams, C. (1978). Ionized hypocalcemia in critically ill patients with sepsis. *Can. J. Surg.*, **21**, 429.

COMPARAISON DES EFFETS DU CHLORURE DE CALCIUM ET DU GLUCEPTATE DE CALCIUM

RESUME

On a comparé les effets du chlorure de calcium et du gluceptate de calcium afin de déterminer leur propriété d'augmentation des concentrations de calcium ionisé dans le plasma [Ca^{2+}]. Pour compenser la faible concentration de calcium ionisé, on a administré à chacun des malades graves d'un groupe de 10 personnes, du chlorure de calcium (10 ml d'une solution à 10%, contenant 27 mg ml^{-1} de calcium élémentaire) et du gluceptate de calcium (20 ml, contenant 18 mg ml^{-1} de calcium élémentaire) pendant 5 mn, dans un ordre déterminé au hasard et à peu près à 6 h d'intervalles. Le [Ca^{2+}] et les éléments hémodynamiques variables (pression artérielle moyenne (MAP), pression moyenne de l'oreillette droite (RAP) et fréquence cardiaque (HR)) ont été surveillés pendant les 30 min qui ont suivi la fin de l'infusion de calcium. L'infusion de l'une ou l'autre préparation de calcium a été associée à des augmentations similaires de [Ca^{2+}] (5 min après l'infusion de chlorure de calcium: 33 ± 3,1%; de gluceptate de calcium: 32 ± 4,3% (moyenne ± écart type des moyennes)) et les effets sur MAP ont été similaires pour chaque solution (11,1 ± 1,8% et 9,7 ± 2,4% respectivement).

VERGLEICHSWEISE WIRKUNGEN VON CHLORKALZIUM UND KALZIUMGLUCEPTAT

ZUSAMMENFASSUNG

Diese beiden Drogen wurden auf ihre Fähigkeit hin verglichen, ionisierte Kalzium-Plasmakonzentrationen [Ca^{2+}] zu erhohen. Um eine niedrige ionisierte Kalziumkonzentration zu korrigieren, erhielten 10 schwerkranke Patienten über eine Periode von 5 Minuten in willkurlicher Reihenfolge je Chlorkalzium (10 ml einer 10%igen Lösung von 27 mg ml^{-1} elementales Kalzium) und Kalziumgluceptat (20 ml, enthaltend 18 mg ml^{-1} elemetales Kalzium), in Abständen von etwa 6 Stunden. [Ca^{2+}] und die hämodynamischen Variablen (mittlerer arteriller Druck (MAP), mittlerer rechtsatrieller Druck (RAP) und Herztatigkeit (HR)) wurden nach Beendigung der Kalziuminfusion auf 30 Minuten überwacht. Die Infusion beider Kalziumpraparate rief ähnliche Anstiege von [Ca^{2+}] hervor (5 min nach Infusion von Chlorkalzium: 33 ± 3,1%; Kalziumgluceptat: 32 ± 4,3% (Mittel ± SEM), und die Wirkungen auf MAP waren bei jeder der beiden Losungen ähnlich (11,1 ± 1,8% und 9,7 ± 2,4%).

EFECTOS COMPARATIVOS DEL CLORURO DE CALCIO Y DEL GLUCEPTATO DE CALCIO

SUMARIO

Se llevó a cabo una comparación de la capacidad del cloruro de calcio y del gluceptato de calcio de incrementar las concentraciones de calcio ionizado en el plasma ([Ca^{2+}]). Con el propósito de corregir una baja concentración de calcio ionizado, se administró a cada uno de 10 pacientes críticamente enfermos tanto cloruro de calcio (10 ml de una solución al 10%, que contenían calcio elemental 27 mg ml^{-1}) como gluceptato de calcio (20 ml, que contenían calcio elemental 18 mg ml^{-1}) en un periodo de 5 min en orden al azar a aproximadamente 6 h de intervalo. Se realizó un control del [Ca^{2+}] y de las variables hemodinámicas (presión arterial media (PAM), presión atrial derecha media (PAD) y del ritmo cárdiaco (RC)) durante un periodo de 30 min después del término de la infusión de calcio. La infusión de cualquiera de las dos preparaciones de calcio se acompañó de aumentos similares en el [Ca^{2+}] (5 min después de la infusión del cloruro de calcio: 33 ± 3,1%; gluceptato de calcio: 32 ± 4,3% (promedio ± SEM) y los efectos sobre el PAM fueron similares para cada solución (11,1 ± 1,8% y 9,7 ± 2,4%, respectivamente).

Br. J. Anaesth. (1980), **52**, 507

CHRONIC HYPERCALCAEMIA SECONDARY TO HYPERPARATHYROIDISM: A RISK FACTOR DURING ANAESTHESIA?

M. A. GUNST AND L. J. DROP

SUMMARY

Hypercalcaemia (increased plasma total calcium concentration; [Ca]) has been associated with serious ventricular arrhythmia and sudden cardiac arrest in patients with hyperparathyroidism. To support our impression that the occurrence of such complications during surgery is rare, we examined the records and e.c.g. of 193 patients with moderate hypercalcaemia ([Ca] = 2.89 ± 0.02 mmol litre^{-1}, mean ± SEM) secondary to histologically demonstrable parathyroid hyperfunction, who were admitted to hospital between 1974 and 1978. We found that ventricular arrhythmia was not recorded for any patient, and A–V junctional rhythm was present at the beginning of operation in two. Before operation a statistically significant although minimal shortening of corrected values of Q–T interval occurred compared with a control group ($n = 60$). However, duration of the corrected Q–T interval was not diagnostic of increased [Ca] in a given patient with hyperparathyroidism.

Hypercalcaemia (abnormal increase in total plasma calcium concentration) in patients with hyperparathyroidism may be considered to increase the risk of anaesthesia (Young and Emerson, 1949; Rapoport, Sepp and Brown, 1960; Surawicz, 1966) because of potentially dangerous disturbances in cardiac rhythm. A manifestation of hypercalcaemia on e.c.g. is the shortening of the Q–T interval (Yu, 1952; Bellet, 1955; Surawicz, 1967a, b).

Dangerous cardiac arrhythmia in patients with hyperparathyroidism during anaesthesia for exploration of the neck seemed to us to be rare. Our impression was that, even when arrhythmia of supraventricular origin was present before operation, major complications resulting from ventricular irritability did not occur during anaesthesia or in the recovery phase. We have studied the occurrence of abnormalities in cardiac rhythm in a large group of patients undergoing parathyroid surgery. We also assessed the duration of the Q–T intervals (QTI) and indices of calcium homeostasis.

PATIENTS

Group 1a ($n = 193$)

Records were reviewed of patients admitted to the Massachusetts General Hospital between 1974 and 1978 with the diagnosis of primary hyperparathyroidism, in whom histological examination of operative specimens revealed the presence of either parathyroid adenoma or hyperplasia. There were 66 male and 127 female patients aged 17–82 yr. Upon admission of each patient, a 12-lead e.c.g. was obtained and venous blood sampled for determination of biochemical variables as part of routine laboratory screening, including plasma total calcium concentration ([Ca]), inorganic phosphorus (P_i), serum potassium and sodium concentrations (K^+ and Na^+, respectively).

Cervical exploration was performed under general anaesthesia. Lead II e.c.g. was displayed on an oscilloscope. Anaesthesia was induced by i.v. infusion of thiopentone (approximately 5 mg kg^{-1}) and the trachea intubated following administration of suxamethonium 1.5 mg kg^{-1}. Anaesthesia was maintained with appropriate concentrations of inhalation anaesthetics (halothane or enflurane) or a combination of morphine or pethidine, droperidol or diazepam, and a nondepolarizing muscle relaxant (pancuronium, tubocurarine or dimethylcurare) and 60% nitrous oxide in oxygen.

Group 1b ($n = 100$)

Records were reviewed of patients admitted to the hospital in the same time period with the diagnosis

---

M. A. GUNST,* M.D.; L. J. DROP, M.D., PH.D.; Anesthesia Services of the Massachusetts General Hospital and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts 02114, U.S.A.

* Present address: Chirurgische Universitätsklinik, Kantonsspital, 4004-Basel, Switzerland.

Correspondence to L. D., Department of Anesthesia, Massachusetts General Hospital, Boston, Massachusetts 02114, U.S.A.

0007–0912/80/050507–05 $01.00

© Macmillan Journals Ltd 1980

of hypercalcaemia unrelated to parathyroid disease. Electrocardiographic and biochemical data were obtained as in group 1a. There were 46 males and 54 females ranging in age between 22 and 86 yr. Conditions associated with hypercalcaemia in these patients are listed in table I.

TABLE I. *Clinical conditions associated with hypercalcaemia (group 1b)*

Carcinoma	58
Lymphoma	8
Multiple myeloma	7
Sarcoidosis	3
Other	24

Group 2 ($n = 60$)

To obtain normal values of QTI and some biochemical variables in a patient population similar to that of group 1a, the records were reviewed of a control group of patients (ASA class I) who underwent operation during 1977 for a variety of surgical procedures. The age range was 28–69 yr and there were no known abnormalities of calcium metabolism. Patients were identified by hospital identification number according to a random number generator.

Patients receiving digitalis preparations or quinidine and those with K^+ or Na^+ values outside the normal range (3.5–5.0 and 135–145 mmol $litre^{-1}$, respectively) were excluded.

METHODS

The 12-lead e.c.g. was recorded at a standard paper speed of 25 mm s^{-1}. The duration of the QTI, determined by averaging three complexes in lead II, was identified and measured according to the method of Lepeschkin and Surawicz (1953). The symbols Q–oT_C and Q–T_C refer respectively to the origin and end of T-wave deflection, measured from the time of the beginning of the Q-wave deflection. Correction for heart rate was made by dividing the duration of the QTI by the square root of the duration of the R–R interval (Bazzett, 1920). Cardiac arrhythmias were identified.

Plasma total calcium concentration ([Ca]) was determined by atomic absorption spectrometry, inorganic phosphorus (P_i) by spectrophotometry, and sodium and potassium concentration by flame photometry. In a few patients plasma ionized calcium concentration ([Ca^{2+}]) was measured by a calcium-selective electrode system (Orion SS 20) at 37 °C as described previously (Drop, Fuchs and Stulz, 1978).

To examine the relationship between QTI and [Ca^{2+}], we determined corrected values of QTI and plasma ionized calcium concentration prospectively in three patients with histologically confirmed primary hyperparathyroidism. In each patient, a 12-lead e.c.g. and a venous blood specimen were obtained upon hospital admission, approximately 30 min before the induction of anaesthesia, immediately following completion of surgery, and daily thereafter up to the second day after operation.

The statistical calculations were performed by use of a programmable calculator (Hewlett-Packard HP 67). Group means were compared by use of Student's *t* test for unpaired data. Values are presented as mean ± SEM.

RESULTS

Group 1*a*. Atrial fibrillation was present on the e.c.g. tracing of one patient before operation (ventricular rate: 60 beat min^{-1}), atrial flutter in one (ventricular rate: 95 min^{-1}). Disturbances in conduction were present before operation on the e.c.g. tracings of 12 patients, including A–V block (first degree) in four patients, and bundle branch block in eight. During operation, the anaesthetist diagnosed A–V junctional rhythm in two patients; and in one of these, lignocaine 1.5 mg kg^{-1} was administered i.v. Ventricular arrhythmias were not identified on any anaesthetic record.

The difference between values of Q–oT_c and Q–T_c in the hyperparathyroid group and those in the control group was minimal (table II), although statistically significant. In three patients, [Ca] and [Ca^{2+}] values were increased before parathyroid exploration, and both values decreased below normal after

TABLE II. *Biochemical variables and corrected Q–T intervals.* * $P < 0.001$ *v. control group;* † $P < 0.01$ *v.* group 1*a*

	Hypercalcaemia		
	Hyperparathyroidism (group 1a)	Other causes (group 1b)	Control (group 2)
[Ca] (mmol $litre^{-1}$)	2.89 ± 0.02*	3.16 ± 0.04*†	2.33 ± 0.01
[P_i] mmol $litre^{-1}$)	0.83 ± 0.01*	1.14 ± 0.04	1.16 ± 0.01
[K^+] (mmol $litre^{-1}$)	4.28 ± 0.03	4.17 ± 0.05	4.28 ± 0.03
Q–oT_c (s)	0.21 ± 0.001*	0.22 ± 0.002	0.22 ± 0.003
Q–T_c (s)	0.38 ± 0.002*	0.40 ± 0.003	0.40 ± 0.003

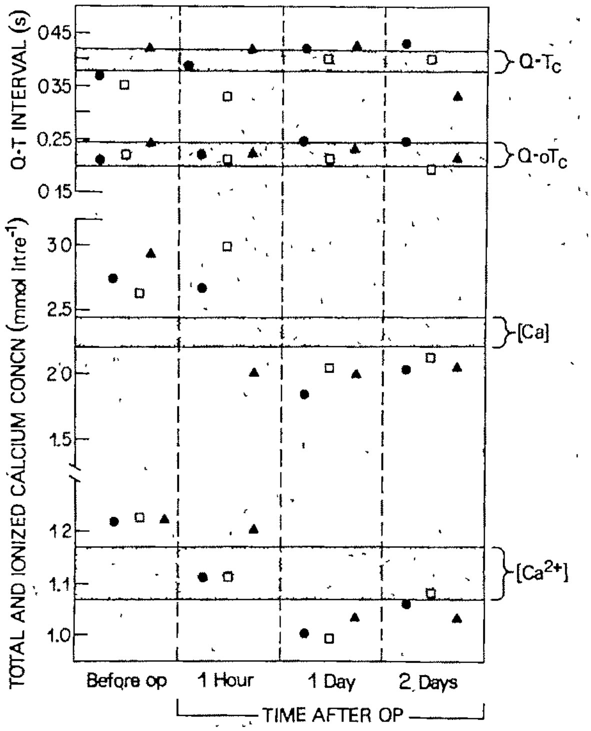


FIG. 1. Time course of corrected Q–T intervals in three patients with hypercalcaemia secondary to parathyroid adenoma. Each data point and each symbol represents one patient. The shaded areas represent the 95% confidence limits of normal. Note that there was no consistent relationship between $[Ca^{2+}]$ and corrected duration of Q–T interval. $[Ca^{2+}]$ = ionized calcium; [Ca] = total calcium.

operation (fig. 1). However, Q–oT_c values were within the normal range throughout the observation period and there was no consistent relationship with $[Ca^{2+}]$ or [Ca].

Group 1b. Abnormalities in cardiac rhythm were identified in two patients (atrial fibrillation with a ventricular rate of 60 and 80 beat min^{-1}); first degree A–V block in one patient, and bundle branch block in seven. [Ca] was greater than in the control group ($P<0.001$) and than in group 1a ($P<0.001$) (table II). However, Q–oT_c and Q–T_c values were not different from the mean values obtained in the control group.

DISCUSSION

In patients with moderate hypercalcaemia secondary to hyperparathyroidism, who underwent surgical exploration of the neck under general anaesthesia, arrhythmia of potential concern occurred in two patients, but ventricular arrhythmia was not recorded.

Payne and Fitchett (1965) have suggested that chronic hypercalcaemia is among factors that may be responsible for serious cardiac complications during anaesthesia for surgery in patients with hyperparathyroidism. Sudden death has been reported in patients with hypercalcaemia secondary to parathyroid hyperfunction (Young and Emerson, 1949; Rapoport, Sepp and Brown, 1960). It has been postulated that such fatal events occur secondary to ventricular fibrillation (Surawicz, 1966). Hypercalcaemia in the experimental animal has also been associated with ventricular premature beats and ventricular fibrillation (Surawicz, 1966). It is known that the duration of the plateau phase (phase 2) of the cardiac action potential is shortened with hypercalcaemia (Surawicz, 1967b). A manifestation of this change in duration of cardiac action potential on e.c.g. is a shortening of QTI (Yu, 1952; Bellet, 1955; Surawicz, 1967a, b). Furthermore, the effective refractory period is shortened and the excitability threshold of the ventricle is increased with hypercalcaemia (Surawicz, 1967a). The combination of decreased conduction velocity (Goodman and Gilman, 1970), increased ventricular excitability and shortening of the ventricular refractory period (Surawicz, 1967a) could facilitate re-entry and the occurrence of ventricular rhythms. If such changes in excitability and conduction occurred, one might expect QTI shortening and potentially serious disturbances in ventricular rhythm in patients with hypercalcaemia. Yet, QTI values in the hyperparathyroid group were shortened only minimally in our study, despite a moderate increase of [Ca], and ventricular arrhythmia was not encountered. It is unlikely that serious disturbances in cardiac rhythm were present but not detected. E.c.g. tracings before operation were interpreted by staff cardiologists from the Cardiac Unit, who always report the presence of ventricular arrhythmias and abnormalities in the duration of the QTI, and by the authors, who were specifically looking for changes in rhythm and time intervals. Even if ventricular arrhythmias were missed on admission to hospital they would be most unlikely to disappear before continuous e.c.g. display during operation. Although it is acknowledged that the anaesthetist may have difficulties in the identification of each occurrence of A–V junctional rhythm from a continuous oscilloscope display of the e.c.g., in this analysis we were interested in the occurrence of any serious cardiac arrhythmias during cervical exploration. If such rhythm disturbances did occur, their appearance and treatment would have been identified on the anaesthetic record. The increase of [Ca] in the hyperparathyroid group was moderate ([Ca] = 2.89 ± 0.02 mmol litre^{-1}). However, mean [Ca] in the patients of group 1b was greater and mean values of QTI in this group were not different from those recorded in the control group. No ventricular arrhythmias were detected on e.c.g. recordings made on admission of these patients. It is possible that more conspicuous changes in QTI and ventricular arrhythmias may occur at [Ca] concentrations substantially greater than those encountered in the present study. Such a possibility would be consistent with previous reports; Yu (1952) reported that QTI shortening was most consistent at [Ca] values that exceeded 3.75 mmol litre^{-1}, while Bronsky and others (1961b) found a consistent QTI shortening in patients with [Ca] values ranging from 3.8 to 6 mmol litre^{-1}. Although the evaluation of the effect of hypercalcaemia on the e.c.g. pattern and the development of cardiac arrhythmias has been difficult in certain circumstances, complete heart block with ventricular escape rhythm at a rate of 40 beat min^{-1} has been described in a patient with [Ca] of 3.87 mmol litre^{-1} (Ginsberg and Schwartz, 1973), and sudden death has been reported in patients with [Ca] values of 4.5 (Jennings et al., 1965) and 5.5 mmol litre^{-1} (Rapoport, Sepp and Brown, 1960).

The serum potassium concentration is known to be a determinant of calcium-induced changes on the duration of Q–T intervals (Surawicz, 1967a). Therefore, in our assessment of e.c.g. manifestations of hypercalcaemia, patients with abnormalities in K^+ concentration were excluded, as were those receiving digitalis (Eliot and Blount, 1961) or quinidine.

In view of the range of corrected QTI values recorded in both control and hyperparathyroid groups (table II), corrected QTI values are not diagnostic of the occurrence of a chronic, moderately increased [Ca]. Similar limitations seem to apply to the reliability of QTI as an index of plasma total calcium during acute changes. Bronsky and others (1961a) found that corrected values of QTI were altered minimally in two patients following calcium loading, increasing [Ca] from 2.8 to 3.5 mmol litre^{-1}. Conversely, Bradlow and Segel (1956) found that Q–T$_c$ remained unchanged in a patient in whom [Ca] decreased from 5.2 to 3.45 mmol litre^{-1} following parathyroid surgery.

Plasma total calcium concentration includes the physiologically active (ionized calcium) and inactive components (complexed and protein-bound calcium) (McLean and Hastings, 1934). Since phase 2 of the cardiac action potential is mainly determined by calcium ion movements across the cardiac cell membrane, changes in the QTI might be expected to correlate with those in plasma ionized calcium ion concentration ([Ca^{2+}]). Results shown in figure 1 are compatible with data by Rumancik and others (1978) who found that QTI was an unreliable index of [Ca^{2+}] in patients during anaesthesia for major surgery in whom rapid fluctuations occurred in [Ca^{2+}] secondary to rapid citrated blood transfusion and calcium chloride infusion. These authors postulated that the Q–T response to rapid [Ca^{2+}] fluctuations might differ from that observed with more gradual [Ca^{2+}] changes such as those recorded in the present study. Our findings cast some doubt on the importance of the time course of [Ca^{2+}] changes in the QTI response to such [Ca^{2+}] changes.

REFERENCES

Bazzett, H. C. (1920). Analysis of time relations of electrocardiograms. *Heart*, **7**, 353.

Bellet, S. (1955). The electrocardiogram in electrolyte imbalance. *Arch. Intern. Med.*, **96**, 618.

Bradlow, B. A., and Segel, N. (1956). Acute hyperparathyroidism with electrocardiographic changes. *Br. Med. J.*, **2**, 197.

Bronsky, D., Dubin, A., Kushner, D. S., and Waldstein, S. S. (1961a). Calcium and the electrocardiogram. The relationship of the intervals of the electrocardiogram to the level of serum calcium. *Am. J. Cardiol.*, **7**, 840.

—— —— Waldstein, S. S., and Kushner, D. S. (1961b). Calcium and the electrocardiogram. The electrocardiographic manifestations of hyperparathyroidism and of marked hypercalcemia from various other etiologies. *Am. J. Cardiol.*, **7**, 833.

Drop, L. J., Fuchs, C., and Stulz, P. M. (1978). Determination of blood ionized calcium in a large segment of the normal adult population. *Clin. Chim. Acta*, **89**, 503.

Eliot, R. S., and Blount, S. G. (1961). Calcium, chelation and digitalis. A clinical study. *Am. Heart J.*, **62**, 7.

Ginsberg, H., and Schwartz, K. V. (1973). Hypercalcemia and complete heart block. *Ann. Intern. Med.*, **79**, 903.

Goodman, L. S.. and Gilman, A. (1970). *The Pharmacological Basis of Therapeutics*, p. 805. New York: Macmillan.

Jennings, E. R., Beland, A. J., Cope, J., Ellestad, M. H., Monroe, C., and Shadle, O. W. (1965). Citrate toxicity and the use of anticoagulant acid citrate dextrose blood for extracorporeal circulation. *Surg. Gynecol. Obstet.*, **120**, 997.

Lepeschkin, E., and Surawicz, B. (1953). The measurement of the Q-T interval of the electrocardiogram. *Circulation*, **6**, 378.

McLean, F. C., and Hastings, A. B. (1934). A biological method for the estimation of calcium ion concentration. *J. Biol. Chem.*, **107**, 337.

Payne, R. L., and Fitchett ,C. W. (1965). Hyperparathyroid crisis. survey of the literature and a report of two additional cases. *Ann. Surg.*, **161**, 737.

Rapoport, A., Sepp, A. H., and Brown, W. H. (1960). Carcinoma of the parathyroid gland with pulmonary metastasis and cardiac death. *Am. J. Med.*, **28**, 443.

Rumancik, W. M., Denlinger, J. K., Nahrwold, M. L., and Falk, R. B. (1978). The Q–T interval and serum ionized calcium. *J.A.M.A.*, **240**, 366.

Surawicz, B. (1966). Role of electrolytes in etiology and management of cardiac arrhythmias. *Prog. Cardiovasc. Dis.*, **8**, 364.

—— (1967a). Arrhythmias and electrolyte disturbances. *Bull. N.Y. Acad. Med.*, **43**, 1160.

—— (1967b). Relationship between electrocardiogram and electrolytes. *Am. Heart J.*, **73**, 814.

Young, L. H., and Emerson, K. (1949). Parathyroid conditions associated with acute parathyroid intoxication. *Ann. Intern. Med.*, **30**, 823.

Yu, P. N. G. (1952). The electrocardiographic changes associated with hypercalcemia and hypocalcemia. *Am. J. Med. Sci.*, **224**, 413.

HYPERCALCEMIE CHRONIQUE DECOULANT DE L'HYPERPARATHYROIDISME: FACTEUR DE RISQUE PENDANT L'ANESTHESIE?

RESUME

L'hypercalcémie (augmentation des concentrations de calcium total dans le plasma[Ca]) a été associée à une sérieuse arythmie ventriculaire et à un arrêt cardiaque soudain chez les malades souffrant d'hyperparathyroïdisme. Pour appuyer l'impression que nous avions, à savoir que l'apparition de ces complications pendant les interventions chirurgicales est rare, nous avons examiné les dossiers et les électrocardiogrammes de 193 patients souffrant d'hypercalcémie modérée ([Ca] =2,89 ± 0,02 mmol litre^{-1}, moyenne ± erreur type des moyennes) découlant de l'hyperfonction parathyroïdienne démontrée histologiquement, et qui étaient entrés à l'hôpital entre 1974 et 1978. Nous avons trouvé qu'aucune arythmie ventriculaire n'avait été enregistrée pour aucun malade, et que le rythme de la commissure auriculo-ventriculaire était présent chez deux personnes au début de l'intervention. Avant l'opération, il s'est produit un raccourcissement d'une importance statistique, des valeurs corrigées de l'intervalle Q–T bien que celui-ci ait été minimal par rapport au groupe témoin (n =60). Toutefois, la durée de l'intervalle Q–T corrigé n'a pas été un diagnostic d'augmentation du [Ca] sur un malade donné souffrant d'hyperparathyroïdisme.

HYPERKALZÄMIE SEKUNDÄR ZU HYPERPARATHYREOIDISMUS: GEFAHRENFAKTOR WÄHREND NARKOSE?

ZUSAMMENFASSUNG

Hyperkalzämie (erhohte Gesamtkonzentration von Kalzium im Plasma) wurde mit schwerer ventrikulärer Arrythmie und plotzlichem Herzstillstand bei Patienten mit Hyperparathyreoidismus in Verbindung gebracht. Um unsere Auffassung zu unterstutzen, dass solche Komplikationen während einer Operation nur selten auftreten, haben wir die Aufzeichnungen über und die EKG's von 193 Patienten untersucht, bei denen massige Hyperkalzamie ([Ca] = 2,89 ± 0,02 mmol Liter^{-1}, Mittelwert ± SEM) sekundär zu einer histologisch nachweisbaren parathyroiden Hyperfunktion gegeben war, und die zwischen 1974 und 1978 ins Krankenhaus eingeliefert worden waren. Eine ventrikulare Arrythmie war für keinen Patienten angegeben, und aurikuläre-ventrikulärer Rhythmus war zu Beginn der Operation bei zwei der Patienten vorhanden. Vor der Operation kam es zu einer deutlichen, wenn auch minimalen Verkürzung der QT–Zeit–Werte im Vergleich mit einer Kontrollgruppe (n =60). Die Dauer der korrigierten QT–Zeit war jedoch kein Anzeichen von erhohtem [Ca] bei Patienten mit Hyperparathyreoidismus.

HIPERCALCEMIA CRONICA COROLARIA AL HIPERPARATIROIDISMO: UN FACTOR DE RIESGOS DURANTE LA ANESTESIA?

SUMARIO

Se ha relacionado la hipercalcemia (concentración total creciente de calcio en el plasma [Ca]) con arritmia ventricular grave y paro cárdiaco repentino en pacientes con hiperparatiroidismo. Para apoyar nuestra impresión de que la ocurrencia de tales complicaciones durante operaciónes quirúrgicas es rara, examinamos los registros y e.c.g. (electrocardiogramas) de 193 pacientes con hipercalcemia moderada ([Ca] = 2,89 ± 0,02 mmol litro^{-1}, promedio ± SEM) corolaria de una hiperfunción paratiróidea histológicamente demostrable, los cuales entraron en el hospital entre 1974 y 1978. Encontramos que no había ninguna arritmia ventricular registrada en relación con algún paciente, un ritmo de junción A–V (auricular–ventricular) se manifestó en dos pacientes al principio de la operación. Antes de la operación, un acortamiento mínimo aunque estadísticamente significativo de los valores corregidos del intervalo Q–T ocurrió en comparación con el grupo de control (n = 60). Sin embargo, la duración del intervalo del Q–T corregido no constituía un diagnóstico del incremento del [Ca] en un paciente dado con hiperparatiroidismo.

Br. J. Anaesth. (1980), **52**, 513

INVESTIGATION OF GLYCOPYRROLATE AS A PREMEDICANT DRUG

A. SENGUPTA, P. K. GUPTA AND K. PANDEY

SUMMARY

The clinical efficacy of glycopyrrolate, a synthetic anticholinergic drug, for premedication was compared in a double-blind study with that of atropine or hyoscine in patients anaesthetized with diethyl ether. The antisialogogue actions of the three drugs were similar. Glycopyrrolate produced less tachycardia, pyrexia and blurred vision than atropine, and its sedative effect was less than that of hyoscine.

Glycopyrrolate (3-1[(cyclopentylhydroxy phenylacetyl) oxy]-1, 1-dimethylpyrrolidinium, (Robinul)) is a potent long-acting anticholinergic drug (Franko and Lunsford, 1960). Ramamurthy, Shaker and Winnie (1972) used this drug with neostigmine to antagonize non-depolarizing neuromuscular blockade and reported that glycopyrrolate prevented excessive salivation and did not cause significant tachycardia. We evaluated glycopyrrolate as a premedicant and compared its antisialogogue and other effects with those of atropine and hyoscine, in patients receiving diethyl ether.

METHODS

One hour before induction of anaesthesia, atropine sulphate 0.6 mg, hyoscine hydrobromide 0.4 mg or glycopyrrolate 0.2 mg was administered on a random, double-blind basis to 90 healthy subjects admitted for minor gynaecological procedures. The patients gave informed consent to the study.

Arterial pressure, heart rate and respiratory frequency were recorded before and at 15-min intervals for 60 min after administration of the premedicant. Oral temperature was recorded and venous blood sampled for estimation of blood sugar concentration and plasma free fatty acids before and 60 min after premedication.

Sedation, lack of apprehension or excitement and dryness of mouth were assessed 60 min after the premedication using criteria described by Dundee and Nicholl (1962) and Feldman (1963). Dizziness, sickness, blurring of vision and pain at the site of injection were noted.

Anaesthesia was induced with nitrous oxide and oxygen (6 : 2 litre min^{-1}) after preoxygenation with 100% oxygen, using a Magill semi-closed circuit. Diethyl ether was added gradually until the patient was adequately anaesthetized. An oropharyngeal airway was inserted.

Observations

During induction:

(1) Excitatory phenomena (muscle tremor and spontaneous movements).
(2) Respiratory disturbances (cough, laryngospasm or bronchospasm).
(3) Troublesome oral secretions (requiring frequent suction).
(4) Vomiting or retching.

Arterial pressure and heart rate were recorded at intervals of 5, 10 and 15 min after induction.

After operation:

(1) Emergence delirium (restlessness and incoherent behaviour during recovery).
(2) Nausea or vomiting (up to 6 h after end of anaesthesia).

Student's t and chi-square tests were used for comparison of means and frequencies of occurrence respectively.

RESULTS

The three groups were comparable in respect of mean age and body weight (table I).

Changes in mean arterial pressure (m.a.p.), and heart and respiratory rate after administration of the three premedicants are shown in table II. A statistically significant increase in m.a.p. was observed in the atropine group at 30, 45 and 60 min. The hyoscine group had a significant increase at 45 min only.

A. SENGUPTA, M.D.; P. K. GUPTA,* M.D., PH.D., D.A.; K. PANDEY, M.D., D.A.; Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India.

* Present address for correspondence: Department of Anaesthesiology, H.P. Medical College, Simla-171001, India.

0007-0912/80/050513-04 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Details of the patients studied*

Premedication	Number	Mean age (yr ± SEM)	Mean body weight (kg ± SEM)
Atropine sulphate 0.6 mg	30	30.73 ± 1.72	51.96 ± 1.13
Hyoscine hydrobromide 0.4 mg	30	31.6 ± 1.83	48.58 ± 1.29
Glycopyrrolate 0.2 mg	30	30.6 ± 1.75	49.2 ± 1.16

Patients in the glycopyrrolate group did not have a significant change in m.a.p.

All three drugs caused a significant increase in heart rate, greatest in the atropine group; an increase in heart rate was observed in hyoscine and glycopyrrolate groups from 30 min onwards (table II).

A significant increase in respiratory frequency was seen in all three groups, least marked in the glycopyrrolate group. The increase in oral temperature was significant in all groups, but was of much greater magnitude following atropine (table III).

TABLE II. *Changes in arterial pressure, heart rate and respiratory rate following administration of the three anticholinergic agents.* **Statistically significant* ($P < 0.05$)

	Control value (before premed.)	Mean changes after premedication			
		15 min	30 min	45 min	60 min
M.a.p. (mm Hg)					
Atropine	88.8 ± 1.60	−0.1 ± 0.28	1.8 ± 0.52*	3.2 ± 0.75*	3.6 ± 0.7*
Hyoscine	86.8 ± 1.58	−0.3 ± 0.19	−0.3 ± 0.20	0.3 ± 0.24*	−0.4 ± 0.24
Glycopyrrolate	90.9 ± 1.72	−0.3 ± 0.25	−0.4 ± 0.26	−0.4 ± 0.26	−0.4 ± 0.24
Heart rate (beat min^{-1})					
Atropine	83.4 ± 1.95	2.2 ± 0.74*	11.6 ± 1.33*	19.2 ± 1.57*	22.3 ± 1.32*
Hyoscine	83.4 ± 2.39	−0.06 ± 0.43	1.8 ± 0.65*	2.4 ± 0.73*	3.1 ± 0.72*
Glycopyrrolate	86.53 ± 2.23	0.2 ± 0.15	3.2 ± 1.05*	5.4 ± 1.56*	8.7 ± 1.63*
Respiratory rate (b.p.m.)					
Atropine	19.3 ± 0.87	0.4 ± 0.6	2.0 ± 0.46*	2.6 ± 0.52*	3.3 ± 0.49*
Hyoscine	17.0 ± 0.49	0.5 ± 0.19*	0.8 ± 0.26*	0.7 ± 0.29*	1.1 ± 0.23*
Glycopyrrolate	18.0 ± 0.74	0.1 ± 0.16	0.3 ± 0.28	0.3 ± 0.30	0.7 ± 0.31*

TABLE III. *Changes in oral temperature* (°C) *in the three study groups* (*mean* ± *SEM*). * $P < 0.05$

	Before premedication	Mean change after premedication
Atropine	36.67 ± 0.038	0.61 ± 0.04
Hyoscine	36.56 ± 0.07	0.06 ± 0.01
Glycopyrrolate	36.72 ± 0.06	0.06 ± 0.01

Mean blood sugar and plasma free fatty acid concentrations increased significantly after premedication in all three groups (table IV). However, the control blood sugar in group III was significantly less than in group I and II, and so no further comparisons of these estimations was made between the groups.

TABLE IV. *Changes in blood sugar and free fatty acid concentrations in the three study groups* (*mean* ± *SEM*). *$P < 0.05$; † *Significantly smaller mean value than groups I and II*

	Blood sugar concn (mmol litre^{-1})		Plasma free fatty acid concn (g litre^{-1})	
	Before premedication	Mean change after premedication	Before premedication	Mean change after premedication
Atropine	4.512 ± 0.159	0.274 ± 0.072*	0.0143 ± 0.0006	0.0025 ± 0.0003*
Hyoscine	4.599 ± 0.239	0.494 ± 0.051*	0.0175 ± 0.0005	0.0022 ± 0.0003*
Glycopyrrolate	4.074 ± 0.136†	0.406 ± 0.061*	0.0163 ± 0.0005	0.0017 ± 0.0003*

TABLE V. *Frequency in the desired and undesired effects of the three study drugs. * Significantly greater frequency than in other groups*

Effects	Atropine	Hyoscine	Glyco-pyrrolate
Desirable:			
Sedation	2	15*	6
Lack of apprehension	26	25	29
Lack of excitement	24	29	30
Dryness of mouth	30	30	30
Undesirable:			
Dizziness	8	5	4
Nausea and vomiting	0	1	0
Pain at site of injection	2	2	2
Blurring of vision	26*	20	14

TABLE VI. *Changes in heart rate and mean arterial pressure during induction (mean ± SEM).* $P < 0.05$

	Heart rate (beat min^{-1})			Mean arterial pressure (mm Hg)		
	Atropine	Hyoscine	Glyco-pyrrolate	Atropine	Hyoscine	Glyco-pyrrolate
Before induction	106.2 ± 2.31	86.53 ± 2.18	92.26 ± 1.38	92.06 ± 1.38	86.16 ± 1.57	90.36 ± 1.76
Mean change after induction:						
5 min	11.9 ± 1.59	9.88 ± 0.99*	12.06 ± 1.18*	6.66 ± 0.53*	7.8 ± 0.63	4.10 ± 0.93*
10 min	11.66 ± 1.69*	10.20 ± 1.03*	14.53 ± 1.58*	7.86 ± 0.79	7.80 ± 0.62*	4.53 ± 0.63*
15 min	4.73 ± 1.91	4.66 ± 0.98*	5.80 ± 1.48*	2.30 ± 0.78	1.83 ± 0.55	1.83 ± 0.62*

TABLE VII. *Observations during anaesthesia and recovery. * Significantly greater frequency in comparison with other groups* ($P < 0.05$)

	Atropine	Hyocine	Glyco-pyrrolate
During anaesthesia			
Excitement	16*	2	9
Respiratory upset	1	0	0
Troublesome secretions	11	15	10
Retching or vomiting	1	1	1
Recovery up to 6 h			
Emergence delirium	0	0	0
Nausea and vomiting	16*	11	6
Troublesome secretions	5	6	5

The frequency of desired and undesired effects are shown in table V. Hyoscine caused sedation more often and atropine caused blurred vision more often in comparison with the other drugs.

During induction and maintenance of anaesthesia a significant increase in the mean heart rate and mean m.a.p. was observed in the three groups at 5-, 10- and 15-min intervals (table VI).

Table VII shows the frequency of different clinical observations during anaesthesia and recovery. More excitatory phenomena were observed in the atropine groups. Troublesome oral secretions were encountered in 33–50% of all the patients, but there was no significant difference between the groups.

In the period immediately after operation, troublesome oral secretions were equally frequent in all three groups. The frequency of nausea and vomiting was significantly greater in the atropine-premedicated group. No serious adverse drug reaction was encountered.

DISCUSSION

The use of anticholinergic drugs in premedication in the Western world is controversial, but their use with ether anaesthesia is essential. The main objects of using these drugs before anaesthesia are to reduce secretion and to inhibit vagal reflexes. The general view is that atropine is a better vagolytic agent than hyoscine, while the latter has the greater antisialogogue action (Wyant and Dobkin, 1957). The results of the present study have shown a more prominent vagolytic action with atropine as demonstrated by marked tachycardia compared with hyoscine or glycopyrrolate, while no significant difference could be detected in the antisialogogue action of the three drugs.

The frequency of nausea or vomiting after surgery in the glycopyrrolate group was significantly less than in the atropine group. Atropine and hyoscine have been shown to possess anti-emetic properties (Riding, 1960) and glycopyrrolate, because of its quaternary ammonium structure, does not cross the blood–brain barrier (Proakis and Harris, 1978). (The lack of central effect such as sedation or excitement might probably be attributed to this property of glycopyrrolate.)

The present study did not provide any information on the duration of action of the three premedicants. It would be interesting to examine the effects of these drugs when combined with sedatives and narcotics given before anaesthesia. It would also be worthwhile to study the effect of glycopyrrolate premedication on the induction of anaesthesia with i.v. agents. The present study has shown glycopyrrolate to be an effective anticholinergic in the circumstances of the study.

ACKNOWLEDGEMENT

We express our gratitude to C. J. Jones of A. H. Robins Company, Horsham, Sussex, U.K., for the supply of glycopyrrolate (Robinul).

REFERENCES

Dundee, J. W., and Nicholl, R. M. (1962). Studies of drugs given before anaesthesia. II: A method for assessing their influence on the course of anaesthesia. *Br. J. Anaesth.*, **34**, 523.

Feldman, S. A. (1963). A comparative study of four premedications. *Anaesthesia*, **18**, 169.

Franko, B. V., and Lunsford, C. D. (1960). Derivations of 3-pyrrolidinols. III: The chemistry, pharmacology and toxicology of some N-substituted-3-pyrrolidyl α-substituted phenylacetates. *J. Med. Pharm. Chem.*, **2**, 523.

Proakis, A. G., and Harris, G. B. (1978). Comparative penetration of glycopyrrolate and atropine across the blood–brain and placental barriers in anaesthetised dogs. *Anesthesiology*, **48**, 339.

Ramamurthy, S., Shaker, M. H., and Winnie, A. P. (1972). Glycopyrrolate as a substitute for atropine in neostigmine reversal of muscle relaxant drugs. *Can. Anaesth. Soc. J.*, **19**, 399.

Riding, J. E. (1960). Post-operative vomiting. *Proc. R. Soc. Med.*, **53**, 33.

Wyant, G. M., and Dobkin, A. B. (1957). Antisialogogue drugs in man. *Anaesthesia*, **12**, 203.

ETUDE DU GLYCOPYRROLATE UTILISE COMME PREMEDICATION

RESUME

On a comparé, au cours d'une étude à double inconnue, l'efficacité clinique du glycopyrrolate, médicament synthétique anticholinergique, utilisé comme prémédication, avec l'efficacité de l'atropine ou de l'hyoscine sur des patients anesthésiés à l'aide d'éther diéthylique. Les actions antisialogogues des trois médicaments ont été similaires. Le glycopyrrolate a produit une tachycardie moins forte, moins de pyrexie et moins de troubles de la vue que l'atropine, et ses effets sédatifs ont été moins forts que ceux de l'hyoscine.

UNTERSUCHUNG VON GLYCOPYRROLAT ALS VORBEHANDLUNGSDROGE

ZUSAMMENFASSUNG

Die klinische Wirksamkeit von Glycopyrrolat, einer synthetischen cholinergischen Droge, als Vorbehandlungsmittel wurde in einem Doppelblind-Versuch mit der von Atropin oder Hyoscin bei Patienten verglichen, die mit Diäthyläther narkotisiert waren. Die speichelhemmenden Wirkungen aller drei Drogen waren ähnlich. Glycopyrrolat rief weniger Tachykardie, Pyrexie und Sichttrübung hervor als Atropin, und seine Sedativwirkung war geringer als die von Hyoscin.

INVESTIGACION SOBRE EL GLICOPIRROLATO COMO SUBSTANCIA DE PREMEDICACION

SUMARIO

Se llevó a cabo una comparación en un estudio doble-ciego de la eficacia clínica del glicopirrolato, una substancia anticolinérgica sintética, para premedicación con la de la atropina o de la hioscina en pacientes anestesiados con éter dietilo. Las acciones antisialógogo de las tres substancias fueron similares. El glicopirrolato produjo menos taquicardia, pirexia y visión borrosa que la atropina, y su efecto sedativo fue menor del de la hioscina.

Br. J. Anaesth. (1980), **52**, 517

I.V. FLUNITRAZEPAM AND I.V. DIAZEPAM IN CONSERVATIVE DENTISTRY

A cross-over trial

R. A. DIXON, N. R. BENNETT, M. J. HARRISON, C. KENYON AND J. A. THORNTON

SUMMARY

In a randomized cross-over trial in 82 outpatients aged 15–45 yr undergoing conservative dentistry, a solution of flunitrazepam 0.25 mg ml^{-1} i.v. (average dose 0.014 mg kg^{-1}) was compared with a solution of diazepam 5 mg ml^{-1} i.v. (0.29 mg kg^{-1}). Cardiovascular changes, operating conditions and side-effects were similar. Forty minutes after the start of injection, about 85% of all patients could not remember the local anaesthetic injection. Thirty minutes after the end of treatment, only 25% of all patients had recovered. One week later, most patients receiving each drug had only vague memories of their treatment; they had felt more relaxed immediately after the i.v. injection than before. Drowsiness was equally common after flunitrazepam and diazepam. Ataxia was more prolonged with flunitrazepam but arm pain and venous thrombophlebitis were less frequent.

Diazepam is widely accepted as a safe anxiolytic and sedative; with i.v. diazepam the degree of anxiolysis and sedation is more precisely controlled than when it is given orally, and there is dense anterograde amnesia immediately following and for about 30 min after injection (Clarke et al., 1970). Unfortunately, i.v. administration of diazepam, even to a large vein, is associated with a high frequency of subsequent thrombophlebitis (Hegarty and Dundee, 1977). Because of poor solubility, reduction of thrombophlebitis by dilution in water is not possible.

Flunitrazepam (Rohypnol: Ro 05–4200), a water-soluble benzodiazepine, is about 20 times more potent than diazepam in its anxiolytic and sedative effects when given i.v. (Stovner, Endresen and Osterud, 1973) and has similar amnesic properties (Dundee and George, 1976).

We have compared the drugs in patients undergoing outpatient conservative dentistry.

METHODS

Admission criteria

The patients were selected either from the waiting list of the Charles Clifford Dental Hospital, Sheffield, or by referral through the Sheffield Student Health Service. The aims of the trial were explained to them. Those who had experienced i.v. sedation for outpatient dentistry previously or who were less than 15 or more than 65 years of age were excluded, as were those for whom only one session of dental treatment was planned. Two patients were admitted to the trial twice for a total of four sessions each. All patients were examined medically, and were considered fit for general anaesthesia. They had fasted as for a general anaesthetic. During treatment they reclined fully in the dental chair. No pack was used in the mouth.

Planning of treatment

The dental surgeon planned for 30 min of dental work at each session.

The first of a repeated series of simple recovery tests (deletion of letters, see below) was carried out at the assessment visit. Where possible, treatment sessions were planned 1 week apart with a further brief visit 1 week later for completion of a questionnaire on attitudes and after-effects, and for polishing of fillings (without sedation).

Recovery: deletion of letters test

Patients were asked to cross out, in 3 min, the letter *p* (but no other letter) on a specially designed sheet containing many lines of jumbled letters (fig. 1). As many lines as possible were completed in this time. The test was made at the medical assessment visit, before each treatment session, and at 10, 20 and 30 min after the end of treatment. Nine different

---

R. A. DIXON, PH.D., Department of Community Medicine, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX. N. R. BENNETT, M.B., CH.B., F.F.A.R.C.S.; M. J. HARRISON,* M.B., B.S., F.F.A.R.C.S.; J. A. THORNTON, M.D., F.F.A.R.C.S., D.A.; Department of Anaesthetics, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX. C. KENYON, B.D.S., Department of Restorative Dentistry, Charles Clifford Dental Hospital, Wellesley Road, Sheffield S10 2SZ.

* Present address: Department of Anaesthesia, Nottingham University Medical School, University Boulevard, Nottingham NG7 2UH.

0007–0912/80/050517-10 $01.00

© Macmillan Journals Ltd 1980

dpoooddbyplldoqqbqlddodyqboybdqylpqyoa
dqapybalodpoldqbyoyp poaplddbqaooybyylp
ldbaqladaqppyylayapadqddybdabydodolboq
ooyobylapbabdllyopappaadldppdbpqoddqqq
pq pdoylqlqaaqblpoyaqd lapbldpdodqaaylda

FIG. 1. Deletion of letter test form: portion of one of nine versions.

designs were used to minimize any learning effect. The first design also included a preliminary "practice line" completed before timing commenced, so that any misunderstanding of instructions could be corrected. (Specimens may be obtained from R. A. D.)

This test has been shown to give a good assessment of recovery of motor function and perception following sedation for dental treatment (Dixon and Thornton, 1973) and was used in three earlier published trials (Cossham and Dixon, 1973; Dixon et al., 1973; Dixon et al., 1976). The number of lines completed in the 3-min period, without consideration of errors, has been found to be the most useful measure for comparing two groups of patients, or for comparing responses after different sedatives within one group. The error rate (number of errors per completed line—omission = single error, deletion of a different letter = double error) (Dixon and Thornton, 1973) was not used as its sensitivity has not been demonstrated. If a drug is associated with "recklessness" (little or no reduction in speed, or even an increase in speed, under the influence of the drug, but an increased error rate) both measures might be tried. When the test is used to determine "street fitness", the error-rate and speed could be determined to detect an atypical "reckless" response to a drug, although only gross increases in error-rate are likely to be significant.

Treatment allocation

At the first treatment the patient was allocated randomly to receive either flunitrazepam or diazepam, after determining whether the initial deletion of letter test score was high or low. The next "high" or "low" allocation envelope was opened by the anaesthetist to determine the identity of the sedative to be administered since it was not possible to conceal this from him. However, neither the dental surgeon nor the monitoring technician was aware of it at any stage. At the second session the alternative drug was used.

Technique of sedation

The dose schedule was arranged so that a person weighing 70 kg would receive diazepam 20 mg (0.29 mg kg^{-1}) or flunitrazepam 1 mg (0.014 mg kg^{-1}), in accordance with the assumed 20-fold difference in potency of the two drugs. An initial dose of either diazepam (Valium 5 mg ml^{-1}) or flunitrazepam in water (0.25 mg ml^{-1}) was administered through an ante-cubital vein at the rate of 1 ml min^{-1} until the weight-related total dose of 0.057 ml kg^{-1}, to the nearest 0.2 ml had been reached. The anaesthetist varied the dose slightly if a patient was clearly under- or over-sedated as the calculated dose was approached as indicated by the usual signs of drooping of the eyelids, loss of consciousness, withdrawal or loss of verbal contact. A local anaesthetic (Xylotox: lignocaine 2%, adrenaline 1 in 80 000) was injected when sedation was established. The operating team attempted to maintain verbal contact with the patient throughout the procedure.

Operating conditions

The dental surgeon assessed (1) ease of administration of the local anaesthetic; (2) ease of access; (3) patient movement; (4) tongue movement. These and the surgeon's overall impression were classified as *good*, *acceptable* or *unacceptable*. Any indication for the use of a mouth prop was recorded. Notes were also made by the dental surgeon or anaesthetist of any adverse reactions such as excessive shivering, tremor, retching or other upset.

Monitoring

The systolic arterial pressure was measured with an East–Radcliffe automatic double-cuff recorder with the cuffs on the left arm. The standard lead II e.c.g. was recorded and from this the heart rate was measured. Oxygen saturation was measured using a Waters XP3 ear oximeter. Apnoeic episodes lasting 30 s or more were identified with a Devices mercury strain gauge.

Measurement of arterial pressure, heart rate and oxygen saturation were made by a monitoring technician (1) before the sedative; (2) 1 min after sedation was established; (3) 1 min after the injection of the local anaesthetic; (4) at 5-min intervals during treatment.

Amnesia

Following dental treatment, 40 min after the i.v. injection, the anaesthetist asked the patient "Can you remember having the injection?" and, if so, "Which one?"

Questionnaire on attitudes and after-effects

A questionnaire was completed by the patient 1 week after each treatment. The formats of the questions are indicated in the appropriate table. The condition of the vein on examination by the anaesthetist, and any other observations were noted at that time. Venous thrombophlebitis was defined as a palpable cord (Hegarty and Dundee, 1977).

RESULTS

The patients

One of 81 patients refused treatment after i.v. injection of diazepam and two patients were readmitted to the trial, contributing four sessions each, so that there were 82 trial admissions. The 43 patients who received diazepam at the first session were comparable to the 39 receiving flunitrazepam in respect of sex, age and weight distribution. Apart from three patients in each treatment group, all returned for a second session of dental treatment under the alternative drug. The age range was 15–45 yr (mean 24 yr), weight 44–86 kg (mean 63 kg); 49 of the 82 were women.

Dosage

Seventy-nine treatment sessions under each drug were available for analysis. At all but 12 sessions for each drug the dose was within 10% of the intended weight-related dosage (table I, fig. 2).

Operating conditions

The drugs produced broadly comparable conditions, ranging from 71 *good* diazepam (DZ) and 67 *good* flunitrazepam (FNTZ) sessions for tongue movement to 57 *good* DZ and 59 *good* FNTZ sessions for access to the mouth; patient movement and ease/difficulty of administration of the local anaesthetic were between these ranges. Overall, the dental surgeons thought that 58 DZ and 63 FNTZ sessions were *good*. A mouth prop was needed at seven DZ and nine FNTZ sessions. Adverse reactions were noted at seven DZ and four FNTZ sessions, no one type of reaction involving more than three patients. These included retching, respiratory obstruction, headache and coughing (with each drug); blurred vision, pallor and perspiration, extensive muscle tremor on e.c.g. (only with DZ); and shivering, dryness of the mouth, depression, dizziness and "very upset" (FNTZ).

TABLE I. *Sedative dosage*

	DZ sessions	FNTZ sessions
Weight-related dose given (mg kg^{-1} body weight)		
Mean	0.276	0.014
Range	0.159–0.333	0.009–0.018
Intended weight-related dose (mg kg^{-1})	0.285	0.014
Patients receiving less than 90% of intended dose	11	8
Patients receiving more than 110% of intended dose	1	4
Total sessions	79	79

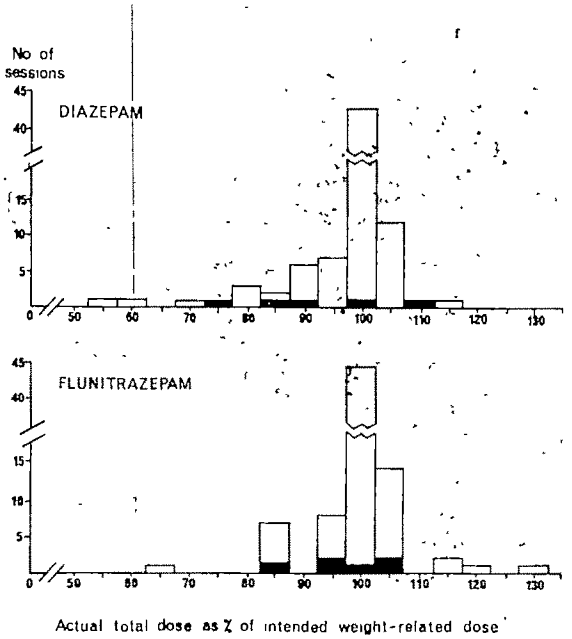


FIG. 2. Adherence to dosage plan, and related distribution of loss of verbal contact for 30 s or longer (filled areas). 79 DZ sessions and 79 FNTZ sessions.

Monitoring

For all sessions (table II) and those at which there was complete monitoring (DZ: 57; FNTZ: 56), the two sedatives were similar as regards changes in systolic arterial pressure, heart rate or oxygen saturation from basal to the arbitrary limits shown.

Verbal contact was lost for 30 s or longer at five diazepam and six flunitrazepam sessions; in none was the dose more than 10% greater than the intended weight-related dose (fig. 2). One or more of the eight events shown in table II occurred at nearly one-quarter of

TABLE II. *Physiological events monitored—number of patients receiving DZ or FNTZ at any monitored time*

	DZ	FNTZ
Arterial pressure increase ≥ 30 mm Hg	—	2
Arterial pressure decrease ≥ 30 mm Hg	4	4
Heart-rate increase ≥ 40 beat min^{-1}	3	3
Heart rate decrease ≥ 40 beat min^{-1}	1	3
O_2 saturation decrease $\geq 5\%$	2	1
Apnoea lasting 30 s or more (by strain gauge only)	1	1
Respiratory obstruction of any duration	2	1
Verbal contact lost for 30 s or more	5	6
At least one of the above changes	16	18
Total no. of sessions	79	79

all sessions, irrespective of treatment. The distributions of change in systolic arterial pressure and in heart rate, relative to pre-treatment, are compared in figure 3. The pattern of change for the two sedatives was similar.

In figure 4, the mean values of arterial systolic pressure, heart rate and oxygen saturation are plotted chronologically for sessions where monitoring equipment was functioning throughout; the two drugs were associated with similar patterns.

Amnesia

Regardless of treatment group, 40 min after the i.v. injection about 10% of patients (seven DZ, six FNTZ) said they could remember neither the local anaesthetic nor the i.v. sedative injections and about 75% (60 DZ, 59 FNTZ) remembered only the i.v. injection.

Recovery

Recovery after surgery (deletion of letter) was tested close to the planned times of 10, 20 and 30 min after completion of the session.

Figure 5 traces the mean value over the nine occasions on which it was administered to the 73 patients who completed all of them. Separate lines are shown for 39 who received DZ at the first session and 34 who received FNTZ. At the 30-min assessment, the mean reduction, compared with the immediate pre-treatment value at that session, was two or three lines, irrespective of the sedative and whether the first or second session is considered. At 10 and at 20 min after treatment, mean reductions relative to pre-treatment values were comparable for each sedative. The pre- to 30-min post-treatment changes in the test score were compared between diazepam and flunitrazepam by means of the Wilcoxon matched-

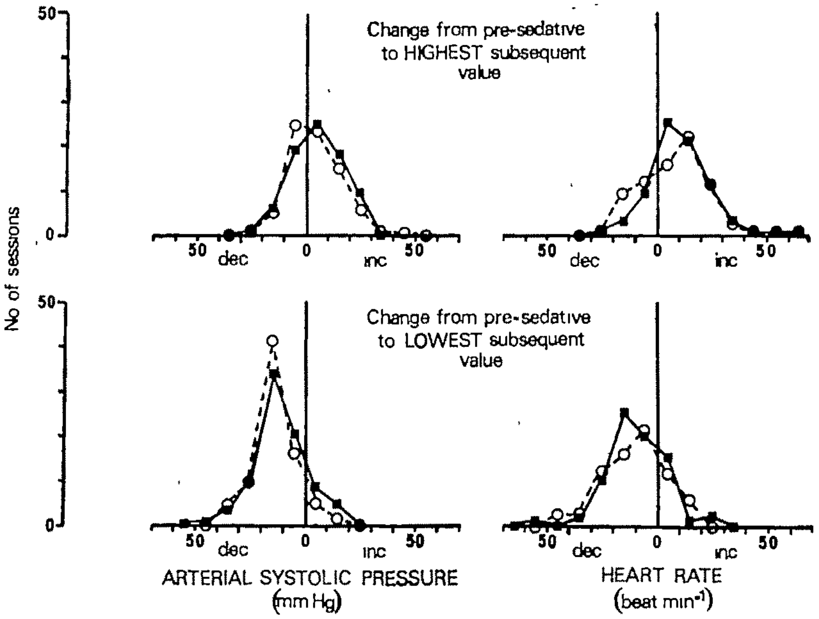


FIG. 3. Monitoring: distributions of changes from pre-treatment values. ■——■ = DZ (79 sessions); ○——○ = FNTZ (79 sessions).

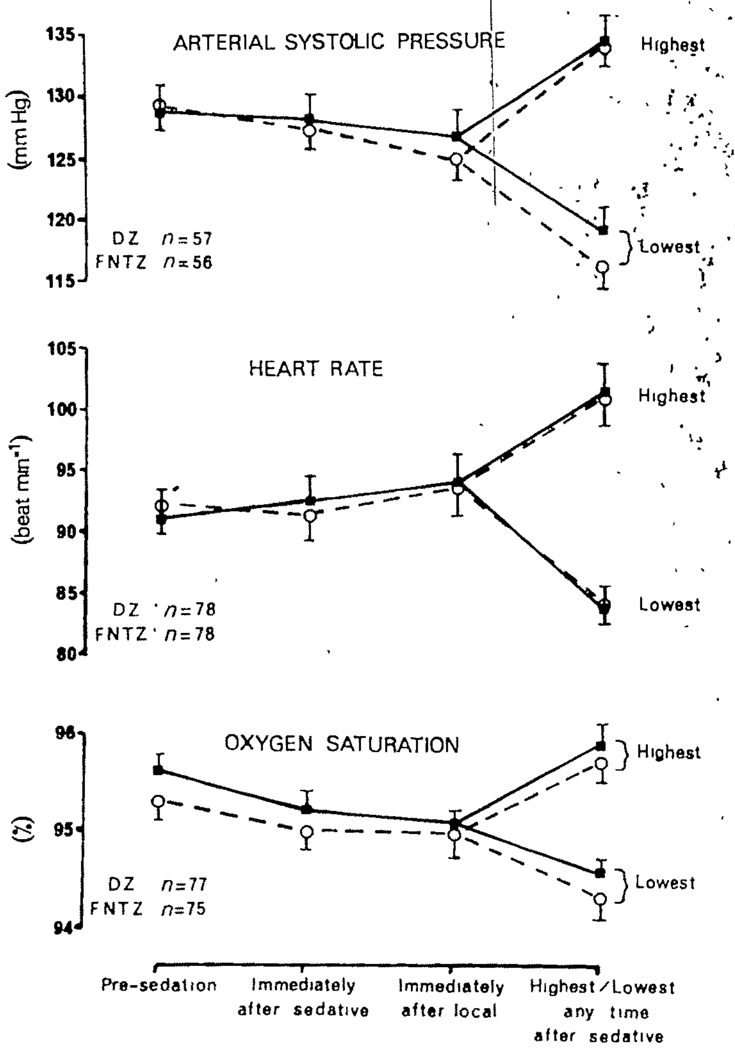


FIG. 4. Monitoring equipment: mean ± SEM at different stages, for sessions with complete monitoring throughout (no. of sessions shown at bottom left of each graph). ■——■ = DZ; ○——○ = FNTZ.

pairs signed ranks test (Siegel, 1956), and the difference between these changes was not significant at the 5% level.

Thirty minutes after the end of treatment under the influence of DZ, 19% of the 73 patients had "recovered" (15% after FNTZ) according to the definition of Dixon and Thornton (1973) which was a post-treatment score at least as great as the larger of the two values recorded at the two most recent tests in the unsedated condition. That is, after the first session, comparison is made with the pre-treatment test and with that of the medical assessment visit; after the second session, with the pre-treatment tests at each of the two sessions.

Ten of the 73 patients had "recovered" earlier after DZ than after FNTZ; six recovered earlier following FNTZ. Two had recovered at the same postoperative test, and 55 (75%) had not recovered at 30 min after either sedative.

Attitudes and after-effects

The replies to the attitude questionnaire 1 week after each session are summarized in tables III and IV. Following three-quarters of the sessions,

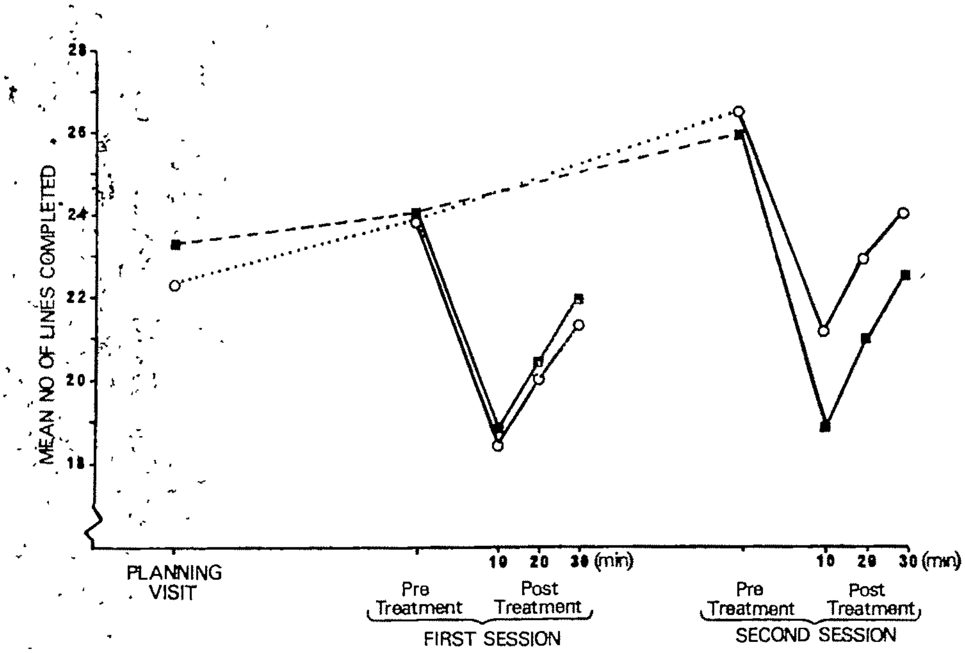


FIG. 5. Deletion of letter test: mean rate of completion at different stages for patients completing all nine tests. ■ - - - ■——■ = DZ at first session FNTZ at second session ($n = 39$); ○ · · · · ○——○ = FNTZ at first session DZ at second session ($n = 34$). (Broken lines denote the "learning curve" joining points at unsedated times.)

irrespective of sedative, patients recalled that after leaving the hospital they had felt drowsy during the first 3 h or so; half of those who received diazepam and two-thirds who received flunitrazepam felt unsteady at this time; with either sedative about 25% felt forgetful; arm pain was reported after about one-third of the diazepam sessions, but rather fewer of the flunitrazepam sessions (see below). Apart from one report of pain lasting 10 days following diazepam, none of these effects lasted more than 24 h. In many respects the answers reflected those to Dixon and others (1976). In particular, a greater proportion of patients were "relaxed" before the second session compared with the first (Q1); most patients felt more relaxed immediately after the i.v. injection (Q2); and most patients had only vague memories of their dental treatment (Q3).

Less common after-effects volunteered in Q5 were: *following DZ*: depression (two), stiff arm (one), general malaise ("no" to Q5 without specific reason) (five); *following FNTZ*: "light-headedness" (two), depression (one), headache (one), rash on face (one), general malaise (six). Almost all patients said they would ask for a sedative again under comparable circumstances. Of those patients attending both dental sessions and expressing a preference for one or other sedative, about two-thirds preferred the first sedative, irrespective of its identity (table IV); this is consistent with findings in previous studies (Cossham and Dixon, 1973; Dixon et al., 1976). In Q7, the patients were specifically asked to make a comparison between the two drugs, but comparisons between the sedatives may be made for every question, by inspection of the answers given with each sedative for those patients who attended the two sessions (table V).

For example, of 25 patients whose responses to Q4b (on unsteadiness) differed between the two sedatives, 18 were "unsteady" on FNTZ but not on DZ; this proportion is not significantly greater than 0.5, the proportion expected if the two sedatives were identical in their ataxic effects (Sign test (Siegel, 1956) $P > 0.05$). However, if the reported duration of the feeling of unsteadiness is also considered, then as many as 45 patients gave different responses on the two occasions; and 32 of these had a longer period of unsteadiness on FNTZ (median time of 1 h extra). These 32 included the 18 who were unsteady after FNTZ but not at all after DZ. This proportion (32/45) differs significantly from the "expected" proportion of 0.5 (Sign test: $P < 0.05$).

TABLE III. *Questionnaire replies*†*: 1 week after each treatment session (numbers of patients, except where shown).*
† *Excluding replies following readmission to trial of two patients.* * *See text for details*

Question	Answers	First session		Second session	
		DZ	FNTZ	DZ	FNTZ
(1) *Before* you had the injection in your arm did you feel:	a. Relaxed	10	9	18	18
	b. A little worried	20	19	12	14
	c. Very anxious	9	7	4	5
	Not recorded	(3)	(3)	(1)	(2)
(2) *After* the injection in your arm did you feel:	a. More relaxed	33	30	24	25
	b. About the same	5	2	8	10
	c. Less relaxed	—	—	—	2
	Not recorded	(4)	(6)	(3)	(2)
(3) How clearly do you remember the fillings being done?	a. Very clearly	4	—	5	8
	b. Only vaguely	23	24	22	21
	c. Not at all	12	11	7	8
	Not recorded	(3)	(3)	(1)	(2)
(4) After you left the hospital, did you:					
(a) feel drowsy?	a. Yes	27	26	28	29
	b. No	12	8	6	8
	Not recorded	(3)	(4)	(1)	(2)
	Median duration (h)	3	3	3	4
(b) feel unsteady?	a. Yes	16	25	21	22
	b. No	22	10	13	13
	Not recorded	(4)	(3)	(1)	(4)
	Median duration (h)	2	1	1	2
(c) feel forgetful?	a. Yes	7	11	10	10
	b. No	32	24	24	26
	Not recorded	(3)	(3)	(1)	(3)
	Median duration (h)	3	1	2	4½
(d) have a sore arm?	a. Yes	12	5	10	4
	b. No	26	30	24	32
	Not recorded	(4)	(3)	(1)	(3)
	Median duration (h)	1½	½	2	½
(5) Apart from any other after effects already mentioned above, did you feel your usual self in the 48 h after treatment?	a. Yes	36	28	28	30
	b. No*	3	6	5	5
	Not recorded	(3)	(4)	(2)	(4)
(6) If a sedative is offered to you again in the form of an injection in the arm will you ask for it?	a. Yes	37	34	33	34
	b. No	2	1	1	2
	Not recorded	(3)	(3)	(1)	(3)
Total number of completed questionnaires		42	38	35	39

TABLE IV. *Sedative preference: 1 week after second session.* * *Excluding replies following readmission to trial of two patients*

Question	Answer	First drug received	
		DZ	FNTZ
(7) You were given a different sedative on the two occasions recently when you had your fillings done. For the benefit of other patients, can you tell us whether you prefer one of the sedatives to the other?	a. No preference	5	5
	b. First sedative—slight preference	6 } 21	7 } 21
	c. First sedative—strong preference	15	14
	d. Second sedative—slight preference	7	5
	e. Second sedative—strong preference	4	3
	f. Not recorded (no polish visit)	(2)	(1)
No. expressing preference for one or other sedative (b, c, d, e)		32	29
Total no. of patients attending *both* dental sessions*		39	35

TABLE V. *Comparison of questionnaire replies after each session. (Patients attending both sessions, excluding replies following readmission to trial of two patients; n = 74).* * For *example, more relaxed (Q1, Q2), or would ask for one sedative but not the other (Q6).* † *Durations of symptoms ignored*

Question	Same response	"More so" after one sedative than other* DZ	FNTZ	Not recorded for one or both sedatives
Q1 Relaxed before i.v. injection?	39	16	16	3
Q2 Relaxed after i.v. injection?	50	9	8	7
Q4 After leaving hospital†:				
(a) drowsy?	49	10	11	4
(b) unsteady?	43	7	18	6
(c) forgetful?	54	6	10	4
(d) arm sore?	49	16	4	5
Q5 Unlike "usual" self?	52	7	9	6
Q6 Would ask for sedative again?	66	2	2	4

TABLE VI. *Arm pain, and the vene-puncture site on examination.* * *Excluding replies following readmission to trial of two patients*

	DZ		FNTZ		Total	
Arm pain reported						
Thrombophlebitis: Yes	8	22	1	9	9	31
No	9		6		15	
Arm not examined	5		2		7	
No arm pain reported						
Thrombophlebitis: Yes	3	50	2	62	5	112
No	34		46		80	
Arm not examined	13		14		27	
Not known whether arm painful		5		6		11
Total no. of completed questionnaires*		77		77		154

Arm pain and venous thrombophlebitis

Of 20 patients with differing answers to the arm pain question (table V), 16 had painful arms after DZ only and the proportion 16/20 is significantly greater than 0.5 (Sign test: $P<0.05$).

The anaesthetist was not always able to be present to examine the arm at about the time the questionnaire was being completed, but failure to do so was as common when the patient reported arm pain (7/31) as when he did not (27/112) (table VI). Following three DZ and two FNTZ sessions, the anaesthetist found a palpable cord at the venepuncture site, indicating venous thrombophlebitis, even though the patient had not reported arm soreness. The symptom of pain was reported after 22 (31%) of the 72 DZ sessions for which this question was answered: 17 of the patients involved had their arms examined by the anaesthetist, who found a palpable cord in eight. Following FNTZ there were nine reports of arm pain (13%); all but two of the patients were examined but only once was a palpable cord found. The pattern is therefore one of less frequent symptoms of arm pain after FNTZ, with even rarer clinical signs of thrombophlebitis, than after DZ.

As in table V, statistical significance is best tested using "within patient" comparisons. Twenty patients reported arm pain following one session but not the other: 16 of these followed DZ and the proportion 16/20 is significantly greater than 0.5 ($P<0.05$). A total of nine patients had palpable cords after one session only: for eight of these patients the sedative given at that session was DZ, but the proportion 8/9 is not significantly different from 0.5 ($P>0.05$). Six patients both reported arm pain and had palpable cords after one session but not the other, and in each instance the drug concerned was DZ. With this small sample size, however, the proportion 6/6 is not significantly greater than 0.5 (Sign test: $P>0.05$).

DISCUSSION

The objectives of controlled sedation in conservative dentistry are to achieve the maximum degree of anxiolysis and sedation commensurate with the maintenance of patient safety and co-operation.

Loss of verbal contact can be regarded as the end-point beyond which control of the patient's airway cannot be guaranteed. To achieve sedation with the ability to maintain verbal contact, it was sometimes necessary to give less than the dose calculated on the basis of body weight and at about 10% of sessions with each sedative less than 90% of this dose was administered. Despite these efforts to control the level of sedation, verbal contact was lost for 30 s or longer at about 7% of the sessions, with each drug.

The drugs were associated with similar proportions of sessions in which any of the measurements of arterial systolic pressure from the recorder varied in either direction by 30 mm Hg or more from basal, or where monitored heart rate varied by 40 beat min^{-1} or more. Provided a dose of about 0.015 mg kg^{-1} of flunitrazepam is used for suitable patients it is likely to be as safe in respect of cardiovascular disturbance, as diazepam at a dose of about 0.030 mg kg^{-1}.

One problem associated with the use of benzodiazepines in outpatients is the slow return to "street-fitness". Thirty minutes after the session, three-quarters of the patients who were treated with both drugs were unable after either to attain the expected normal response to the simple test which has been taken as an index of recovery. After leaving the hospital, drowsiness, unsteadiness and forgetfulness were common. Since the two benzodiazepines are not associated with an acceptable return to street fitness within the time a patient would normally be present in a dental surgery, every patient should be accompanied home by a fit adult and advised not to indulge in any hazardous activity such as driving a car for at least 24 h* after the intravenous injection.

The high frequency of thrombophlebitis following the administration of diazepam is well recognized, particularly if the injection is given into a small vessel. In this study, 1 week after treatment, arm pain was reported by 31% of patients following diazepam, and by 13% following flunitrazepam. Twenty patients who reported arm pain following one sedative reported none after the other sedative and in 16 such instances diazepam was given at the session where the arm pain was reported. It is not clear whether these differences can be attributed to the insolubility of diazepam in water, or to a possible irritant effect of its solvent.

Anterograde amnesia is an added bonus associated with the i.v. administration of the benzodiazepines and is particularly valuable in dentistry as it can cover the unpleasant period associated with the injection of the local anaesthetic. Irrespective of the sedative used, about 85% of patients could not remember the local anaesthetic, and 1 week later most had only vague memories of their dental treatment. As in two previous studies (Cossham and Dixon, 1973; Dixon et al., 1976), the only preference for one or other sedative, expressed by patients 1 week after the second session, was for the first sedative offered. In all three studies, of a total of 174 patients given i.v. diazepam and asked (in similar but not identical questions) about the value to them of i.v. sedation, all but 11 implied that they would ask for it for future dental work. In each study there is evidence of a more relaxed attitude to their dentistry in a high proportion of the patients when attending for their *second* session (in this paper see table III, question (1)). It therefore seems likely that i.v. sedation may well reclaim some nervous patients for unsedated conservation work, and this could be tested by means of an appropriate addition to the questionnaire.

In other respects the two sedatives were associated with similar side- and after-effects, with the exception of more prolonged ataxia following flunitrazepam. Against this, arm pain and venous thrombophlebitis occurred less frequently with flunitrazepam.

REFERENCES

Clarke, P. R. F., Eccersley, P. S., Frisby, J. P., and Thornton, J. A. (1970). The amnesic effect of diazepam (Valium). *Br. J. Anaesth.*, **42**, 690.

Cossham, P. S., and Dixon, R. A. (1973). Subanaesthetic dosage of propanidid as a sedative for dentistry: a controlled clinical trial. *Br. J. Anaesth.*, **45**, 369.

Dixon, R. A., Atkinson, R. E., Kenyon, C., Lamb, D., Thornton, J. A., and Woodhead, S. (1976). Subanaesthetic dosage of Althesin as a sedative for conservative dentistry: a controlled trial. *Br. J. Anaesth.*, **48**, 431.

—— Day, C. D., Eccersley, P. S., and Thornton, J. A. (1973). Intravenous diazepam in dentistry: monitoring results from a controlled clinical trial. *Br. J. Anaesth.*, **45**, 202.

—— Thornton, J. A. (1973). Tests of recovery from anaesthesia and sedation: intravenous diazepam in dentistry. *Br. J. Anaesth.*, **45**, 207.

Dundee, J. W., and George, K. A. (1976). The amnesic action of diazepam, flunitrazepam and lorazepam in man. *Acta Anaesthesiol. Belg.*, **27**, (Suppl. 3), 3.

Hegarty, J. E., and Dundee, J. W. (1977). Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam and flunitrazepam. *Br. Med. J.*, **2**, 1384.

Siegel, S. (1956). *Nonparametric Statistics for the Behavioural Sciences.* (International student edition.) Tokyo: McGraw-Hill Kogakusha Ltd.

Stovner, J., Endresen, R., and Østerud, A. (1973). Intravenous anaesthesia with a new benzodiazepine Ro5-4200. *Acta Anaesthesiol. Scand.*, **17**, 163.

ADMINISTRATION INTRAVEINEUSE DE FLUNITRAZEPAM ET DE DIAZEPAM POUR LES TRAITEMENTS DENTAIRES CONSERVATEURS

Essais avec inversion des séries

RESUME

Au cours d'essais effectués au hasard, avec inversion des séries, sur 82 patients de consultation externe âgés de 15 à 45 ans, et recevant des soins dentaires conservateurs, on a comparé les effets de l'administration intraveineuse d'une solution de flunitrazépam à raison de 0,25 mg ml^{-1} (dose moyenne 0,014 mg kg^{-1}) avec ceux découlant de l'administration intraveineuse d'une solution de diazépam à raison de 5 mg ml^{-1} (dose moyenne 0,29 mg kg^{-1}). Les variations cardiovasculaires, les conditions d'opération et les effets secondaires ont été similaires. Quarante minutes après le commencement de l'injection, environ 85% des patients ne se souvenaient plus de l'injection anesthésiante locale.

---

* The interval recommended by the British Medical Association after general anaesthesia is 48 h—*Editor.*

Trente minutes après la fin du traitement, seulement quelque 25% des patients avaient retrouvé leurs esprits. Une semaine plus tard, la plupart des patients recevant chaque drogue n'avaient que de vagues souvenirs de leur traitemente; ils s'étaient sentis plus détendus immédiatement après l'injection intraveineuse qu'avant. La somnolence diurne a été tout aussi courante après le flunitrazépam qu'après le diazépam. L'ataxie a été plus longue avec le flunitrazépam, mais la douleur au bras et la thrombophlébite veineuse ont été moins fréquentes.

INTRAVENÖS GEGEBENES FLUNITRAZEPAM UND DIAZEPAM BEI KONSERVIERENDER ZAHNBEHANDLUNG

ZUSAMMENFASSUNG

Bei einem willkürlichen Kreuzversuch mit 82 ambulanten Patienten zwischen 15–45 Jahren und konservierender Zahnbehandlung wurde eine intravenos verabreichte Losung von Flunitrazepam 0,25 mg ml^{-1} (Durchschnittsdosis 0,014 mg kg^{-1}) verglichen mit einer intravenosen Diazepam-Lösung von 5 mg ml^{-1} (0,29 mg kg^{-1}). Herzkreislaufveränderungen, Arbeitsbedingungen und Nebenerscheinungen waren bei beiden Losungen ähnlich. Viersig min nach Injektionsbeginn konnten rund 85% aller Patienten sich nicht mehr an die Lokalanasthesie erinnern. Dreissig min nach Ende der Behandlung hatten sich nur 25% der Patienten von der Anästhesie erholt. Eine Woche danach hatten die meisten Patienten nur mehr vage Erinnerungen an ihre Behandlung; sie waren sofort nach der intravenosen Injektion entspannter gewesen als vorher. Schläfrigkeit trat auf Flunitrazepam ebenso häufig auf wie auf Diazepam. Ataxie war langer dauernd bei Flunitrazepam, aber Armschmerzen und venose Thrombophlebitis waren weniger häufig.

FLUNITRAZEPAM I.V. Y DIAZEPAM I.V. EN ODONTOLOGIA CONSERVADORA

Un ensayo de cruce

SUMARIO

En un ensayo cruce al azar sobre 82 pacientes ambulatorios de 15 a 45 años de edad sometidos a odontología de conservación, se comparó una solución de flunitrazepam de 0,25 mg ml^{-1} i.v. (dosis promedia—0,014 mg kg^{-1}) con una solución de diazepam de 5 mg ml^{-1} i.v. (0,29 mg kg^{-1}). Los cambios cardiovasculares, las condiciones de la operación y los efectos colaterales fueron similares. Cuarenta minutos después del principio de la inyección, alrededor del 85% de los pacientes no podían acordarse de la inyección anestética local. Treinta minutos después del fin del tratamiento, se había recuperado el 25% de los pacientes únicamente. Una semana después, la mayoría de los pacientes recibiendo cada droga sólo tenían vagos recuerdos de su tratamiento; se sintieron más relajados inmediatamente después de la inyección i.v. que antes. La somnolencia fue de igual modo común después del flunitrazepam y del diazepam. La ataxia fue más prolongada con el flunitrazepam pero los dolores en el brazo y la tromboflebitis venosa fueron menos frecuentes.

Br. J. Anaesth. (1980) **52,** 527

COMPARISON OF THE CARDIOVASCULAR EFFECTS OF BOLUS *V.* INCREMENTAL ADMINISTRATION OF THIOPENTONE

J. L. SELTZER, J. I. GERSON AND F. B. ALLEN

SUMMARY

Twenty unpremedicated patients (ASA grade I) were assigned randomly to receive thiopentone in 50-mg increments every 15 s until loss of lash reflex (group I) or as a 4-mg kg^{-1} bolus (group II). Arterial pressure, heart rate, systolic time intervals and end-tidal carbon dioxide were measured in the control state and then every 30 s. The mean dose of thiopentone in group I was 5.58 ± 1.24 (SD) mg kg^{-1} which was significantly larger than in group II ($P < 0.001$). Both groups exhibited similar decreases in arterial pressure and increases in heart rates. The degree of cardiac depression revealed from measurement of the systolic time intervals, indexed for heart rate, was equal in the two groups.

Fieldman, Ridley and Wood (1955) have stated that the incremental administration of thiopentone, at a rate of 50 mg min^{-1}, will induce general anaesthesia without producing decreases in arterial pressure. However, their conclusion is open to question. Their patients were premedicated and were receiving nitrous oxide while the thiopentone was being administered and the measurements made. In addition, carbon dioxide tensions were neither measured nor controlled.

In clinical practice, thiopentone is injected usually as a bolus of 4–6 mg kg^{-1} or given at a more rapid incremental rate than was used in Fieldman's study. We have compared the cardiovascular effects of a bolus of thiopentone with those of an incremental injection technique.

METHODS

This study was approved by The Committee for the Protection of Human Subjects at our institution and written informed consent was obtained from each patient. Twenty unpremedicated patients (ASA grade I) were assigned randomly to receive thiopentone incrementally at a rate of 50 mg per 15 s (group I) or as a bolus of 4 mg kg^{-1} (group II). Control measurements of arterial pressure (BP) by the Riva–Rocci method, heart rate (HR) as determined by the R–R interval on the e.c.g., systolic time intervals (STI) and end-tidal carbon-dioxide ($F\text{E}'_{CO_2}$) were recorded while the patients breathed 100% oxygen from a face-mask. Measurements of STI were made from a simultaneous 100-mm s^{-1} recording of the e.c.g., phonocardiogram and carotid arterial pulse tracing. Recordings were made on a Hewlett-Packard (HP) 78308A recorder. The phonocardiogram was obtained with an HP 21050A contact sensor placed in that area of the precordium which produced the finest tracing. An HP 21051D pulse-wave pickup was placed on the neck to record the carotid pulse tracing. $F\text{E}'_{CO_2}$ were obtained from a precalibrated Beckman LB-2 Medical Gas Analyzer.

Group I patients received thiopentone 50 mg every 15 s until the lash reflex was abolished. Group II patients received thiopentone 4 mg kg^{-1} as a bolus injected as rapidly as possible through an 18-gauge i.v. cannula. Haemodynamic measurements were recorded in each group when a total of thiopentone 4 mg kg^{-1} had been given and every 30 s thereafter. Recordings were continued for 5 min or until the patients showed signs of wakening. Oxygen 100% was continued and ventilation of the lungs was assisted if necessary to maintain a $F\text{E}'_{CO_2}$ between 4.5% and 5.5% throughout the study.

Total electromechanical systole (QS$_2$), left ventricular ejection time (LVET) and HR were averaged from three to five sinus heart beats in each measurement period. The pre-ejection period (PEP) was calculated as QS$_2$ minus LVET and all values were indexed for HR (Weissler, Harris and Schoenfeld, 1968). From the indexed values of QS$_2$ (QS$_2$-I) and LVET (LVET-I), 1/PEP^2-I and PEP-I/LVET-I were calculated to determine the effect of the thiopentone on myocardial function. The maximum changes in BP, HR, 1/PEP^2-I and PEP-I/LVET-I

JOSEPH L. SELTZER, M.D.; JOHN I. GERSON, M.D.; FORREST B. ALLEN, M.D.; Department of Anesthesiology, SUNY—Upstate Medical Center, 750 E. Adams Street, Syracuse, N.Y. 13210, U.S.A.

0007–0912/80/050527–04 $01.00

© Macmillan Journals Ltd 1980

were compared between the two groups using a two-tailed unpaired *t* test.

RESULTS

Comparison of the control states in both groups showed no differences (table I) and control values of STI were consistent with accepted values (Weissler, Harris and Schoenfeld, 1969). In every patient, a decrease in arterial pressure and a depression of cardiac function, as indicated by STI, occurred during the study period, with subsequent recovery towards control values. The mean dose of thiopentone in group I was 5.58 ± 1.24 (SD) mg kg^{-1} which represented a significantly larger dose than the 4 mg kg^{-1} received by group II ($P < 0.001$). All but one patient in group II lost the lash reflex with the 4-mg kg^{-1} bolus. Table II shows that both groups experienced similar decreases in arterial pressure and increases in heart rate. No significant difference in the degree of cardiac depression, as revealed by changes in 1/PEP^2-I and PEP-I/LVET-I, was evident between the groups. The period during which the patients in both groups remained unconscious varied. Group I patients slept for 150–300 s with a mean of 264 ± 60 s. Group II slept for 60–300 s with a mean of 222 ± 94 s. The difference between groups was statistically ($P < 0.05$) but probably not clinically significant.

TABLE I. *Control data (mean ± SD) for the two thiopentone groups. Group I v. group II: none of the differences significant ($P > 0.05$) by two-tailed unpaired t test. For abbreviations see text.*

	Group I (incremental)	Group II (bolus)
Systolic BP (mm Hg)	122.5 ± 20.3	123.5 ± 10.81
Diastolic BP (mm Hg)	69.5 ± 9.56	75.0 ± 8.5
Heart rate (beat min)	80.2 ± 18.4	70.5 ± 14.0
1/PEP-I^2 (s^{-2})	58.55 ± 11.22	61.73 ± 13.81
PEP-I/LVET-I	0.314 ± 0.031	0.312 ± 0.034

TABLE II. *Maximum changes from control (mean ± SD) in the two thiopentone groups. Values in parentheses represent % change from control. None of the differences group I v. group II significant ($P > 0.05$) by two-tailed unpaired t test*

	Group I (incremental)	Group II (bolus)
Systolic BP decrease (mm Hg)	14.2 ± 8.28 (11.6)	16.00 ± 5.68 (12.9)
Diastolic BP decrease (mm Hg)	5.70 ± 7.30 (8.2)	9.00 ± 6.99 (12)
Heart rate increase (beat min^{-1})	11.52 ± 12.56 (14.3)	15.89 ± 3.89 (22.5)
1/PEP^2-I decrease (s^{-2})	11.02 ± 8.26 (17.5)	15.12 ± 10.95 (22.5)
PEP-I/LVET–I increase	0.033 ± 0.026 (10.6)	0.045 ± 0.026 (14.8)

DISCUSSION

Several groups of investigators have described the effect of thiopentone on myocardial function as determined by STI (List, 1975; Dauchot et al., 1976; Filner and Karliner, 1976; Becker and Tonnesen, 1978). In all these studies the patients received atropine. In two, either diazepam (Filner and Karliner, 1976) or pethidine (List, 1975) was administered also before the study period. In none of these studies were various modes of administration of thiopentone compared.

Externally measured STI have been shown to correlate well with invasively obtained indices (Martin et al., 1971). Prolongation of PEP has been shown to correlate with decreases in stroke volume and cardiac output (Weissler, Harris and Schoenfeld, 1968, 1969) while 1/PEP^2 has been compared with peak ascending aortic blood-flow acceleration and has been shown to have a good correlation with the latter (Reitan et al., 1972). Therefore, a decrease in 1/PEP^2 indicates a decrease in myocardial contractility. An increase in the ratio of PEP/LVET indicates a decrease in left ventricular function (Weissler, Harris and Schoenfeld, 1969). In subjects without valvular disease, shunts or cor pulmonale Ahmed and colleagues (1972) demonstrated a good correlation of PEP/LVET to ejection fraction and cardiac index and excellent correlation to measurements of myocardial contractility.

In spite of the fact that the patients in group I received about 40% more thiopentone than those in group II, we could not demonstrate any significant difference in the cardiovascular effects of these two modes of administration of thiopentone. A possible explanation for the larger dose given to group I is that the blood concentration necessary to abolish the lash reflex is reached more slowly as a result of constant redistribution of the incremental doses. When the blood concentration was obtained, it was probably very close to that obtained with the bolus and, therefore, the cardiovascular side-effects were similar. It is likely that a larger bolus (6 mg kg^{-1})

would produce greater peak blood concentrations which would lead to further myocardial depression. If so, a difference might be demonstrated between this large bolus (6 mg kg^{-1}) and the type of incremental induction described.

As our results are based on findings in healthy patients, we caution against extrapolation of these results to high-risk patients such as those who are hypovolaemic or in heart failure. Hypovolaemia would allow anaesthetic blood concentrations to be reached after a much smaller dose of thiopentone than is described here. List (1975) has shown that digitalis improves STI measured after thiopentone when compared with measurements made in the same patients 1 week before receiving digitalis. One can infer from List's work that patients with various degrees of left ventricular dysfunction show a greater degree of myocardial depression following thiopentone than those with normal myocardial contractility.

We conclude that inducing anaesthesia to the point of abolishing the lash reflex in healthy patients by giving thiopentone incrementally at a rate of 50 mg per 15 s produces cardiovascular depression similar to that seen following a 4 mg kg^{-1} bolus.

ACKNOWLEDGEMENT

The authors wish to thank Ms Frances Kriese for her excellent technical assistance during this study.

REFERENCES

Ahmed, S. S., Levinson, G. E., Schwartz, C. J., and Ettinger, P. O. (1972). Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. *Circulation*, **46**, 559.

Becker, K. E., and Tonnesen, A. S. (1978). Cardiovascular effects of plasma levels of thiopental necessary for anesthesia. *Anesthesiology*, **49**, 197.

Dauchot, P. J., Rasmussen, J. P., Nicholson, D. H., Divers, R. T., Katona, P. G., Zollinger, R. M., Knoke, J. D., Kyo, E. W., and Gravenstein, J. S. (1976). On-line systolic time intervals during anesthesia in patients with and without heart disease. *Anesthesiology*, **44**, 472.

Fieldman, E. J., Ridley, R. W., and Wood, E. H. (1955). Hemodynamic studies during thiopental sodium and nitrous oxide anesthesia in humans. *Anesthesiology*, **16**, 473.

Filner, B. E., and Karliner, J. S. (1976). Alterations of normal left ventricular performance by general anesthesia. *Anesthesiology*, **45**, 610.

List, W. F. (1975). Digitalis–thiopentone effects on myocardial function. *Anaesthesia*, **30**, 624.

Martin, C. E., Shaver, J. A., Thompson, M. E., Reddy, P. S., and Leonard, J. J. (1971). Direct correlation of external systolic time intervals with internal indices of left ventricular function in man. *Circulation*, **44**, 419.

Reitan, J. A., Smith, N. T., Borison, V. S., and Kadis, L. B. (1972). The cardiac pre-ejection period: a correlate of peak ascending aortic blood-flow acceleration. *Anesthesiology*, **36**, 76.

Weissler, A. M., Harris, W. S., and Schoenfeld, C. D. (1968). Systolic time intervals in heart failure in man. *Circulation*, **37**, 149.

——— ——— ——— (1969). Bedside technics for the evaluation of ventricular function in man. *Am. J. Cardiol.*, **23**, 577.

COMPARAISON DES EFFETS CARDIO-VASCULAIRES: BOL PAR RAPPORT A ADMINISTRATION PROGRESSIVE DE THIOPENTONE

RESUME

Vingt malades n'ayant reçu aucun prétraitement (ASA grade 1) ont été désignés au hasard pour recevoir des doses de thiopentone augmentant progressivement par paliers de 50 mg toutes les 15 s, jusqu'à ce qu'ils perdent le réflexe cilaire (groupe I) ou sous la forme d'un bol de 4 mg kg^{-1} (groupe II). On a mesuré la pression artérielle, la fréquence cardiaque, les intervalles des systoles et le gaz carbonique en fin d'expiration à l'état témoin et ensuite toutes les 30 s. La dose moyenne de thiopentone du groupe I a été de 5,58 ± 1,24 (écart type) mg kg^{-1}, ce qui a été sensiblement plus important que dans le groupe II ($P < 0{,}001$). On a constaté dans les deux groupes des baisses de pression artérielle et des augmentations de fréquence cardiaque similaires. Le degré de dépression cardiaque qui est ressorti de la mesure des intervalles des systoles indéxés pour la fréquence cardiaque, a été le même pour les deux groupes.

VERGLEICH DER HERZKREISLAUF-WIRKUNGEN BEI BOLUS- ODER SCHRITTWEISER VERABREICHUNG VON THIOPENTON

ZUSAMMENFASSUNG

Zwanzig nicht vorbehandelte Patienten (ASA grade I) wurden willkürlich ausgewählt, Thiopenton 50 mg alle 15 s zu erhalten, bis Verlust des Lidreflexes auftrat, (gruppe I), oder als Bolus zu 4 mg kg^{-1} (gruppe II). Arterieller Druck, Herztatigkeit, systolische Intervalle und Ausatmungs-Kohlendioxidgehalt wurden im Kontrollstadium und dann alle 30 s gemessen. Die mittlere Thiopenton-Dosis in gruppe I betrug 5,58 ± 1,24 (SD) mg kg^{-1}, was wesentlich mehr war als in gruppe II ($P < 0{,}001$). Beide Gruppen zeigten ähnliches Absinken des arterillen Druckes und Anstiege der Herztatigkeit. Das Ausmass der kardialen Depression, festgestellt durch Messung der systolischen Zeitintervalle gemäss der Herztätigkeit, war in beiden Gruppen gleich.

COMPARACION DE LOS EFECTOS CARDIOVASCULARES DE UN BOLO DE TIOPENTONA CON LA ADMINISTRACION PROGRESIVA DE LA MISMA

SUMARIO

Se designó a veinte pacientes que no habían recibido premedicación (ASA Grado I) al azar para recibir tiopentona en incrementos de 50 mg cada 15 s hasta pérdida del

reflejo ciliar (grupo I) o como un bolo de 4 mg kg^{-1} (grupo II). Se llevó a cabo la medición de la presión arterial, del ritmo cárdiaco, de los intervalos sistólicos y el dióxido de carbono terminal-respiratorio en el estado de control y después cada 30 s. La dosis media de tiopentona en el grupo I era de 5,58 ± 1,24 (SD) mg kg^{-1}, lo que representa una dosis significativamente mayor de la del grupo II ($P < 0{,}001$). Ambos grupos manifestaron similares disminuciones de la presión arterial y aumentos de los ritmos cárdiacos. El grado de depresión cárdiaca arrojada por la medición de los intervalos sistólicos puestos en índice para el ritmo cárdiaco era igual para los dos grupos.

Br. J. Anaesth. (1980) **52**, 531

PANCURONIUM IN CAESAREAN SECTION AND ITS PLACENTAL TRANSFER

E. ABOULEISH, L. B. WINGARD JR, S. DE LA VEGA AND N. UY

SUMMARY

Pancuronium bromide was used in 49 patients undergoing repeat elective Caesarean section. In 26 patients who received only pancuronium 0.1 mg kg^{-1}, pancuronium was detected in all umbilical venous or arterial samples (0.12 μg ml^{-1}). In 23 other patients who received suxamethonium 1.0 mg kg^{-1} followed by pancuronium 0.05 mg kg^{-1}, pancuronium was detected in fetal blood 2 min after injection; the concentration of pancuronium in umbilical venous or arterial samples in 14 subjects was 0.08 μg ml^{-1}, and less than 0.05 μg ml^{-1} in nine subjects. There was no evidence that such concentrations of pancuronium were detrimental to the fetus. The use of suxamethonium before pancuronium resulted in reduction of pancuronium dosage, induction–delivery time, and fetal concentrations of pancuronium, and was associated with better condition of the neonate.

Pancuronium is used increasingly for muscle relaxation during obstetric anaesthesia because of less cardiovascular depression (Neeld et al., 1974) and less histamine release (Dobkin, Arandia and Levy, 1973) compared with tubocurarine. Spiers and Sim (1972), using suxamethonium followed by pancuronium 0.07–0.10 mg kg^{-1}, detected pancuronium and its metabolites in the urine of 11 of 20 infants, using a methyl orange–spectrophotometric assay procedure of limited sensitivity (0.6 μg ml^{-1} from 5.0 ml of urine). The patients were unselected and included those undergoing emergency operations. Urine samples were stored before assay. In a subsequent study, Heaney (1974) attempted to detect pancuronium in fetal serum using a low sensitivity bioassay, but did not obtain clear results.

The most recent studies of the placental transfer of pancuronium and metabolites were by Booth, Watson and McLeod (1977), and by Duvaldestin and others (1978); both studies were conducted with the more sensitive rose bengal–fluorimetric assay for pancuronium and metabolites (Kersten, Meijer and Agoston, 1973). In both studies, suxamethonium was used for intubation followed by pancuronium 0.058 mg kg^{-1} (Booth, Watson and McLeod, 1977) and 0.050–0.080 mg kg^{-1} (Duvaldestin et al., 1978). Pancuronium and its metabolites were detected at delivery in umbilical plasma from all 11 subjects in the 1977 study (0.04–0.1 μg ml^{-1}, mean 0.07 μg ml^{-1}) and in umbilical vein serum from all 33 subjects in the 1978 study (0.04–0.14 μg ml^{-1}, mean 0.07 μg ml^{-1}). In both of these studies, some of the patients suffered from hypertension or had undergone emergency delivery which might have influenced the placental transfer of pancuronium. In addition, the authors did not indicate the duration and conditions under which plasma or serum samples were held before assay. This is an important point, since we have observed a significant decrease in the apparent concentration of pancuronium and metabolites, using the rose bengal–fluorimetric assay, when serum samples were refrigerated or frozen for more than 12 h (Wingard et al., 1979). In addition, the fluorescence stability of the rose bengal–pancuronium complex apparently is difficult to control as judged by the inability of ourselves (Wingard et al., 1979) and Watson and McLeod (1977) to use the original method (Kersten, Meijer and Agoston, 1973) without modification. Although a sensitivity of 0.02 μg ml^{-1} has been claimed for the Kersten, Meijer and Agoston (1973) pancuronium-plus-metabolite method, evidence of the variability and reproduction of the assay results has not been presented to support this degree of sensitivity. From an analysis of our modified rose bengal–fluorimetric technique we have concluded that the minimum reliably measured serum concentration of pancuronium and metabolites is 0.05 μg ml^{-1} (Wingard et al., 1979).

E. ABOULEISH, M.B., CH.B., M.D.; S. DE LA VEGA, M.D.; N. UY, M.D.; Department of Anesthesiology. L. B. WINGARD JR, PH.D., Departments of Anesthesiology and Pharmacology. University of Pittsburgh School of Medicine and Magee-Womens Hospital.

Correspondence to E. A., Magee-Womens Hospital, Pittsburgh, Pa 15213, U.S.A.

0007-0912/80/050531-06 $01.00

© Macmillan Journals Ltd 1980

The present study was to determine the extent of placental transfer of pancuronium, when used alone or following suxamethonium, with the pancuronium assay performed using our modified technique and carried out within 6 h after sampling. Only patients free from maternal and fetal complications were included.

METHODS

Forty-nine patients were undergoing elective repeat Caesarean section. They were healthy, 38–40 weeks pregnant, not receiving medication, and without fetal compromise or distress. The plan of study was approved by the Human Research Committee of Magee-Women's Hospital, and all patients gave informed consent.

The patients were premedicated with hydroxyzine HCl 1 mg kg^{-1} i.m. 1 h before surgery.

Group I

The mean age and weight of the 26 patients were 26.6 ± 1.1 (SEM) yr and 67.5 ± 2.1 kg. Pancuronium, the sole muscle relaxant, was administered in a dose of 0.1 mg kg^{-1} of the full-term maternal weight. A few minutes before induction of anaesthesia, left uterine displacement was performed, atropine 0.4 mg was injected i.v., oxygen was administered, and monitoring was established (see below). Induction of anaesthesia consisted of thiopentone 4 mg kg^{-1} followed by cricoid pressure, pancuronium i.v. and lung ventilation using 100% oxygen. When paralysis was adequate, tracheal intubation was performed, the cuff inflated and cricoid pressure released. Anaesthesia was maintained with 66% nitrous oxide in oxygen. After the umbilical cord was clamped, nitrous oxide was supplemented by morphine 0.2 mg kg^{-1} and diazepam 0.1 mg kg^{-1} (Abouleish and Taylor, 1976). In all patients, at the end of the surgical procedure, residual paralysis was antagonized with atropine 1 mg and neostigmine 2.5 mg; additional neostigmine, in 1-mg doses, was injected when required.

Group II

The mean age and weight of the 23 patients were 27.5 ± 0.9 yr and 75.0 ± 2.5 kg. Suxamethonium was used for intubation and the dose of pancuronium reduced to 0.05 mg kg^{-1}. Following injection of thiopentone, suxamethonium 1 mg kg^{-1} was injected i.v., followed by tracheal intubation. When recovery of the muscle twitch occurred, pancuronium 0.05 mg kg^{-1} was administered with further doses of pancuronium injected after delivery when required. The maintenance of anaesthesia and patient monitoring were the same as in group I.

Maternal monitoring included heart rate, arterial pressure, e.c.g. and neuromuscular transmission using peripheral nerve stimulation. At delivery, the condition of the baby was evaluated by a neonatal paediatrician who was unaware of the muscle relaxant used. At the time of delivery, blood samples were taken for maternal arterial, umbilical venous and umbilical arterial $P\mathrm{o}_2$, $P\mathrm{co}_2$ and acid–base determinations.

For assay of pancuronium, 5-ml samples of non-heparinized blood were collected from the maternal vein immediately before the induction of anaesthesia (control) and from the maternal artery and vein at the time of delivery. Since there was no statistically significant difference between the pancuronium concentrations in the maternal arterial and venous sera in group I, arterial blood sampling for pancuronium was omitted in group II. Umbilical venous and arterial samples also were collected at the time of delivery from a double-clamped segment of the umbilical cord.

The sera were assayed for pancuronium using our modified fluorimetric procedure (Wingard et al., 1979). The assay measured total pancuronium plus metabolites. Serum samples that showed marked haemolysis were discarded because of high readings of fluorescence intensity. The fluorimetric procedure gave reliable measurements of pancuronium to a lower limit of 0.05 μg ml^{-1} (Wingard et al., 1979); and apparent concentrations at smaller values were excluded from the results and calculations. No interference by the other drugs was noted at pancuronium serum concentrations of 0.05 μg ml^{-1} for hydroxyzine hydrochloride 50 μg ml^{-1}, atropine 0.08 μg ml^{-1}, sodium thiopentone 56 μg ml^{-1}, suxamethonium 1.0 μg ml^{-1} and choline 10.0 μg ml^{-1}.

The results are reported as the mean ± SEM. Comparison of means was made using paired or non-paired Student's t tests, with a P value of 0.05 or less chosen to denote a significant difference.

RESULTS

In both groups anaesthesia was satisfactory, relaxation was adequate and the antagonism of paralysis at the end of the operation was readily obtained. Maternal arterial $P\mathrm{o}_2$, $P\mathrm{co}_2$ and acid–base status were normal. Only some increases in maternal heart rate (10–20%) and maternal arterial pressure (4–8%) were noted.

In group I (pancuronium 0.1 mg kg^{-1}), the mean concentration of pancuronium in the maternal venous and maternal arterial sera were 0.51 ± 0.04 μg ml^{-1} and 0.52 ± 0.04 μg ml^{-1} respectively ($P > 0.3$). All the infants were mature, with a mean weight of 3059 ± 87 g. Pancuronium was detected in a concentration of 0.05 μg ml^{-1} or more in all cord blood samples, with identical mean umbilical venous and arterial values of 0.12 ± 0.01 μg ml^{-1}. The fetal concentrations of pancuronium were significantly less than in the mother ($P < 0.001$), giving an umbilical venous to maternal venous ratio of 0.26 ± 0.03. The mean time between pancuronium injection and delivery was 12.9 ± 0.8 min; the time from uterine incision to delivery was 1 min or less in 20 patients, and 1–2 min in six patients. The Apgar scores are shown in table I. Comparing those infants with a 1-min Apgar score of 6 or less with those of 7 or more, there were no statistical differences in pancuronium concentrations in umbilical vein or umbilical artery. All the neonates in group I, except one, had Apgar scores of 7 or more at 5 min.

TABLE I. *Apgar scores. Group I = pancuronium 0.1 mg kg^{-1}; group II = suxamethonium 1.0 mg kg^{-1} + pancuronium 0.05 mg kg^{-1}. * Lower frequency in group II compared with group I ($P < 0.05$); ** greater frequency in group II compared with group I ($P < 0.05$)*

	1-min		5-min	
Scores	Group I ($n = 26$)	Group II ($n = 23$)	Group I ($n = 26$)	Group II ($n = 32$)
0–3	1	2	0	0
4–6	10*	1*	1	2
7–10	15**	20**	25	21

In group II (suxamethonium 1.0 mg kg^{-1} followed by pancuronium 0.05 mg kg^{-1}) the concentration of pancuronium in the maternal venous serum at the time of delivery was 0.42 ± 0.04 μg ml^{-1}. This value was not significantly different from that in group I despite the marked reduction in the pancuronium dosage, probably because of the significantly shorter time from pancuronium injection to delivery in group II. All the infants were mature with a mean weight of 3204 ± 83 g, which was not significantly different from those of group I. The umbilical venous and arterial pancuronium concentrations ranged from less than 0.05 to 0.15 μg ml^{-1}; the mean of the values 0.05 μg ml^{-1} or more was 0.08 ± 0.01 μg ml^{-1} for either the arterial or venous samples. These values were significantly less than the maternal serum concentrations ($P < 0.001$), giving an umbilical venous to maternal venous ratio of 0.21 ± 0.02. The pancuronium fetal concentrations for group II, even after exclusion of concentrations less than 0.05 μg ml^{-1}, were much smaller than those for group I ($P < 0.004$). In group II, the pancuronium–delivery time was 4.2 ± 0.4 min, significantly shorter than in group I. The uterine incision–delivery time was 1 min or less in 14 patients, 1–2 min in seven patients and 2–3 min in two patients. Although the 1-min Apgar scores were better in group II than in group I, the 5-min scores were similar (table I). In both groups, $P\text{O}_2$, $P\text{CO}_2$ and acid–base status of the infants at the time of delivery were normal (table II); however, the umbilical arterial pH and base excess were significantly greater for the infants in group II (table II).

TABLE II. *Acid–base state, $P\text{O}_2$ and $P\text{CO}_2$ at time of delivery. Group I = pancuronium 0.1 mg kg^{-1}; group II = suxamethonium 1.0 mg kg^{-1} + pancuronium 0.05 mg kg^{-1}. * Significant statistical difference ($P < 0.025$) between groups I and II; ** significant statistical difference ($P < 0.002$) between groups I and II*

	Group I		Group II	
	Mean	SEM	Mean	SEM
Maternal arterial blood				
pH (unit)	7.39	0.02	7.40	0.01
$P\text{a}_{\text{O}_2}$ (kPa)	19.2	0.77	17.5	0.79
$P\text{a}_{\text{CO}_2}$ (kPa)	4.27	0.16	4.0	0.15
Base excess (mmol litre^{-1})	−4.0	0.5	−4.7	0.4
Umbilical venous blood				
pH (unit)	7.31	0.01	7.31	0.01
$P\text{O}_2$ (kPa)	4.09	0.23	3.96	0.19
$P\text{CO}_2$ (kPa)	5.60	0.16	5.99	0.14
Base excess (mmol litre^{-1})	−5.1	0.4	−4.0	0.3
Umbilical arterial blood				
pH (unit)	7.25*	0.01	7.28*	0.01
$P\text{O}_2$ (kPa)	2.50	0.20	2.53	0.13
$P\text{CO}_2$ (kPa)	6.43	0.15	6.53	0.13
Base excess (mmol litre^{-1})	−6.5	0.6	−4.0**	0.4

In both groups, the maternal concentrations of pancuronium decreased at an approximate first order rate as the time from pancuronium injection to delivery became longer (fig. 1). The mean half-lives were 29 min in group I and 8 min in group II. It would have been more useful to obtain pancuronium half-life values from each patient; however, we could not justify the additional blood sampling as providing

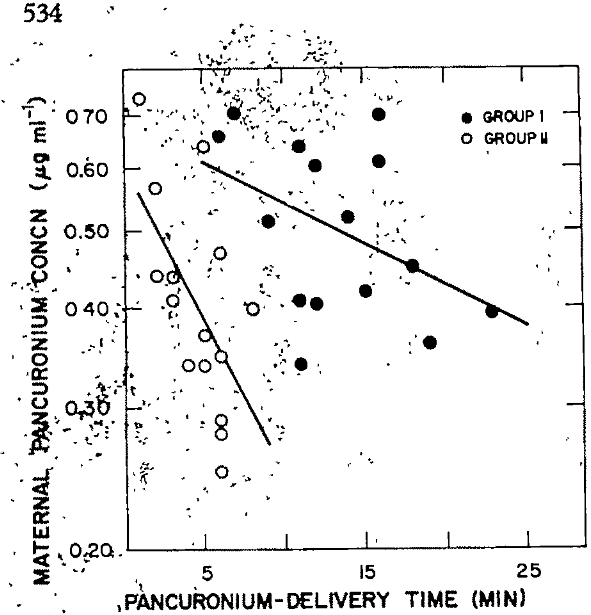


FIG. 1. Logarithm of the maternal serum concentration of pancuronium at delivery as a function of the time between pancuronium injection and delivery. Group I, pancuronium 0.1 mg kg^{-1} only; group II, suxamethonium 1 mg kg^{-1} followed by pancuronium 0.05 mg kg^{-1}. Lines fitted by linear least squares.

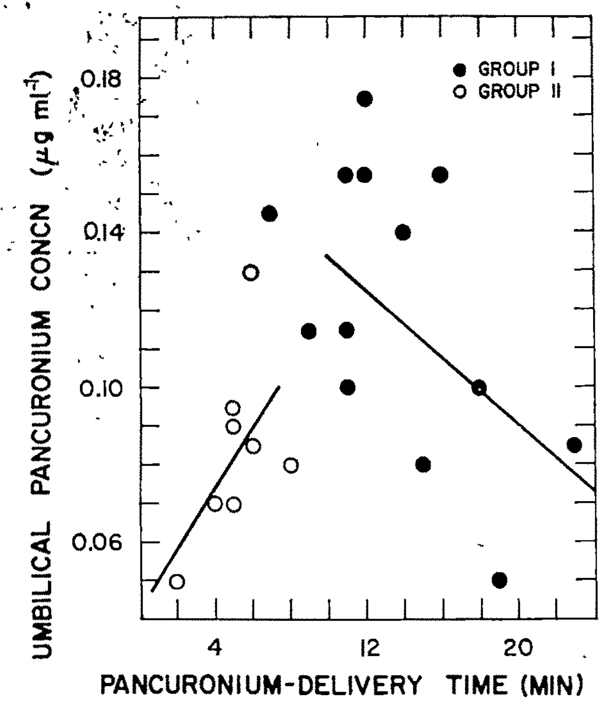


FIG. 2. Umbilical concentration of pancuronium at delivery following different time intervals between pancuronium injection and delivery. Symbols as in figure 1. Lines fitted by linear least squares.

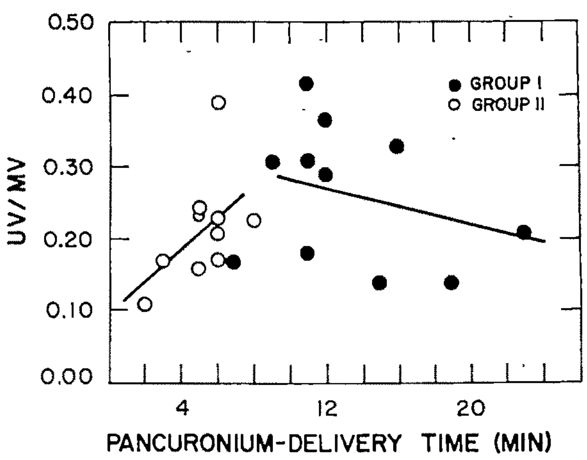


FIG. 3. Umbilical venous to maternal venous ratio of pancuronium at delivery following different time intervals between pancuronium injection and delivery. Symbols as in figure 1. Lines fitted by linear least squares.

any benefit to the patient and thus were limited to the method described. Since the correlation coefficients of groups I and II were only 0.4 and 0.6 respectively for the data in figure 1, the resulting half-lives can be taken only as estimates.

In group II, pancuronium was observed in umbilical venous and arterial sera within 2 and 3 min respectively following injection into the maternal circulation. Moreover, the umbilical concentration of the drug increased with longer pancuronium–delivery times (fig. 2). In group I, with a greater dose of pancuronium and longer pancuronium–delivery times, the umbilical pancuronium concentrations decreased with longer injection–delivery times (fig. 2). Since the correlation coefficient for either group of data in figure 2 was 0.5, the lines must be taken as estimates; nevertheless, there does appear to be a trend within each group.

The umbilical venous to maternal venous ratio showed an increase with pancuronium–delivery time in group II ($r = 0.52$) (fig. 3). Although in group I the same ratio decreased with time, the correlation was poor ($r = 0.29$).

DISCUSSION

The results show that, in normal repeat elective Caesarean section, pancuronium administered to the mother crossed the placenta rapidly to give, at delivery, an umbilical to maternal serum concentration ratio of 0.26 (group I) and less than 0.21 (group II).

The main difference with pancuronium instead of suxamethonium for intubation was that both the pancuronium dose and the pancuronium–delivery time were greater when only pancuronium was used; thus a larger quantity of pancuronium was exchanged across the placenta.

During the first few minutes after administration of pancuronium, the umbilical concentrations of pancuronium would be expected to be very small, providing a concentration difference across the placenta for net pancuronium transfer from mother to fetus. This was shown in group II when delivery coincided with that short period. At longer times (group I), the umbilical pancuronium concentration would be expected to decrease, possibly because of reversal of the maternal to fetal gradient of the free fraction of pancuronium or redistribution to and uptake of the drug by the fetal tissues, or both. It should be noted that the umbilical to maternal ratio of pancuronium also increased and then decreased.

The slightly more acidic blood in group I was probably attributable to the greater time between induction and delivery, causing some degree of aortocaval compression despite efforts to displace the uterus to the left (table III).

TABLE III. *Doses (mg) and time intervals (min). Group I = pancuronium* 0.1 *mg* kg^{-1}; *group II = suxamethonium* 1.0 *mg* kg^{-1} + *pancuronium* 0.05 *mg* kg^{-1}. * *Significant statistical difference between groups I and II* ($P < 0.05$)

	Group I ($n = 26$)		Group II ($n = 23$)	
	Mean	SEM	Mean	SEM
Dose of pancuronium before delivery	6.6	0.2	3.8*	0.1
Total dose of pancuronium	6.6	0.2	4.5*	0.3
Total dose of neostigmine	2.8	0.2	2.6	0.1
Thiopentone–delivery time	13.5	0.9	8.7*	0.4
Pancuronium–delivery time	12.9	0.8	4.2*	0.4
Pancuronium–neostigmine time	57.2	2.5	51.0	3.2
Operation time	57.8	2.2	55.3	3.2

It is of particular interest to relate the umbilical concentrations of pancuronium to the estimated degree of neuromuscular blockade in the neonate, as an indication of the margin of safety for the mean umbilical concentrations of 0.12 µg ml^{-1} (group I) and less than 0.08 µg ml^{-1} (group II). It is well known that, in maternal and fetal blood, part of the drug is bound to plasma proteins and is not available for exchange across the placenta, which is determined by the relative concentrations of the unbound portions. Also, the unbound portion of a drug, rather than its total mass, determines its pharmacological activity. Agoston and others (1977) found that 50% blockade occurred in adults at a bound-plus-unbound pancuronium concentration of 0.11 µg ml^{-1}. However, Goudsouzian, Ryan and Savarese (1974) found that infants and children may require a larger dose of pancuronium than adults to achieve the same degree of paralysis. In our study, there was no evidence that the umbilical pancuronium concentrations were detrimental to the neonate. Yet, similarities between the umbilical serum pancuronium concentrations observed at delivery, and the serum concentrations needed for 50% blockade in adults, point strongly to the need for determining the relative concentrations of unbound pancuronium in maternal and fetal sera. It is also important to determine the relationship between the concentration of unbound pancuronium in the umbilical serum and the degree of neuromuscular blockade in the neonate. Moreover, the effect of edrophonium on the neonatal muscle twitch following administration of non-depolarizing muscle relaxants to the mother, and its possible role in neonatal resuscitation would be interesting future studies.

The low 5-min Apgar scores in three of 42 neonates were most probably a result of factors other than pancuronium because the fetal serum concentrations of the drug in these three babies did not differ significantly from the others in the groups and the duration of apnoea and the need for resuscitation was less than 10 min. The frequency of low Apgar scores in our study was comparable to similar studies using pancuronium (Heaney, 1974; Booth, Watson and McLeod, 1977; Duvaldestin et al., 1978), tubocurarine (Neeld et al., 1974), or suxamethonium (Marx, Cosmi and Wollman, 1969).

In conclusion, our study confirmed the adequacy and safety of pancuronium for Caesarean section. It demonstrated the rapid transmission of the drug across the placenta and the development of appreciable concentrations in the fetal blood. It also showed that suxamethonium for tracheal intubation before pancuronium enabled us to reduce the dose of pancuronium, the induction–delivery time and the fetal blood concentrations of the drug.

ACKNOWLEDGEMENTS

The authors acknowledge the financial support of the Organon Co. for the conduct of this work. The Prophet Computer System of NIH was used for analysis of the data. The authors extend their gratitude to Mr Daniel West for technical assistance and Mrs Margie Faller for secretarial assistance.

REFERENCES

Abouleish, E., and Taylor, F. H. (1976). Effect of morphine-diazepam on signs of anesthesia, awareness, and dreams of patients under N_2O for Cesarean section. *Anesth. Analg.* (*Cleve.*), **55**, 702.

Agoston, S., Crul, J. F., Dersten, U. W., and Scaf, A. H. J. (1977). Relationship of the serum concentration of pancuronium to its neuromuscular activity in man. *Anesthesiology*, **47**, 509.

Booth, P. N., Watson, M. J., and McLeod, K., (1977). Pancuronium and the placental barrier. *Anaesthesia*, **32**, 320.

Dobkin, A. B., Arandia, H. Y., and Levy, A. A. (1973). Effect of pancuronium bromide on histamine levels in man. *Anesth. Analg.* (*Cleve.*), **52**, 772.

Duvaldestin, P., Demetriou, M., Henzel, D., and Desmonts, J. M. (1978). The placental transfer of pancuronium and its pharmacokinetics during Caesarean section. *Acta Anaesthesiol. Scand.*, **22**, 327.

Goudsouzian, N. G., Ryan, J. F., and Savarese, J. J. (1974). The neuromuscular effects of pancuronium in infants and children. *Anesthesiology*, **41**, 95.

Heaney, G. A. H. (1974). Pancuronium in maternal and foetal serum. *Br. J. Anaesth.*, **46**, 282.

Kersten, U. W., Meijer, D. K. F., and Agoston, S. (1973). Fluorimetric and chromatographic determination of pancuronium bromide and its metabolites in biological materials. *Clin. Chim. Acta.*, **44**, 59.

Marx, G. F., Cosmi, E. V., and Wollman, S. B. (1969). Biochemical states and clinical condition of mother and infant at Cesarean section. *Anesth. Analg.* (*Cleve.*), **48**, 986.

Neeld, J. B., Seabrook, P. D. jr, Chastain, G. M., and Frederickson, E. L. (1974). A clinical comparison of pancuronium and tubocurarine for Cesarean section anesthesia. *Anesth. Analg.* (*Cleve.*), **53**, 7.

Spiers, I., and Sim, A. W. (1972). The placental transfer of pancuronium bromide. *Br. J. Anaesth.*, **44**, 370.

Watson, M. J., and McLeod, K. (1977). A modified method for the fluorimetric determination of pancuronium bromide in plasma. *Clin. Chim. Acta*, **79**, 511.

Wingard, L. B. jr, Abouleish, E., West, D. C., and Goehl, T. J. (1979). Modified fluorimetric quantitation of pancuronium bromide and metabolites in human maternal and umbilical serums. *J. Pharm. Sci.*, **68**, 914.

LE PANCURONIUM ET SON TRANSFERT PLACENTAIRE LORS DES OPERATIONS CESARIENNES

RESUME

On a utilisé du bromure de pancuronium sur 49 personnes subissant à nouveau une opération césarienne à froid. Sur les 26 personnes auxquelles on n'avait administré que du pancuronium, à raison de 0,1 mg kg^{-1}, on a décelé du pancuronium dans tous les échantillons ombilicaux veineux ou artériels (0,12 $\mu g\ ml^{-1}$). Sur les 23 autres personnes auxquelles on avait administré du suxaméthonium, à raison de 1 mg kg^{-1}, puis du pancuronium, à raison de 0,05 mg kg^{-1}, on a décélé du pancuronium dans le sang du foetus 2 mn après l'injection; la concentration de pancuronium dans les échantillons ombilicaux veineux ou artériels a été de 0,08 $\mu g\ ml^{-1}$ sur 14 sujets, et de moins de 0,05 $\mu g\ ml^{-1}$ sur 9 autres. Il n'a pas été prouvé que de telles concentrations de pancuronium étaient préjudiciables au foetus. L'usage de suxaméthonium avant le pancuronium a entraîné une réduction des doses de pancuronium, une réduction de l'intervalle induction–accouchement; de même qu'une réduction des concentrations de pancuronium dans le foetus; on a également constaté que le nouveau-né se portait mieux.

PANCURONIUM BEI KAISERSCHNITT UND ÜBERTRAGUNG DER DROGE AUF DIE PLAZENTA

ZUSAMMENFASSUNG

Pancuroniumbromid wurde bei 49 Patientinnen bei wiederholtem Kaiserschnitt verwendet. Bei 26 Patientinnen, die nur Pancuronium 0,1 mg kg^{-1} erhielten, wurde die Droge in sämtlichen venösen oder arteriellen Nabelschnur-Blutproben (0,12 $\mu g\ ml^{-1}$) entdeckt. Bei den 23 anderen Patientinnen, die Suxamethonium 1,0 mg kg^{-1} erhielten, gefolgt von Pancuronium 0,05 mg kg^{-1}, wurde Pancuronium 2 min nach der Injektion im fötalen Blut festgestellt; die Drogenkonzentration in venösen oder arteriellen Nabelschnur-Blutproben betrugen bei 14 Patientinnen 0,08 $\mu g\ ml^{-1}$, und weniger als 0,05 $\mu g\ ml^{-1}$ bei 9 Patientinnen. Es gab kein Beweis dafur, dass derartige Pancuronium-Konzentrationen für den Fotus schädlich waren. Die Verwendung von Suxamethonium vor Pancuronium fuhrte zur Verringerung der Pancuronium-Dosis, der Zeit zwischen Verabreichung und Geburt, und auch der Konzentrationen von Pancuronium; gleichzeitig eine bessere Verfassung der Neugeborenen.

EL PANCURONIO EN OPERACION CESAREA Y SU TRANSFERENCIA PLACENTAL

SUMARIO

Se usó bromuro de pancuronio en 49 pacientes sometidas a una operación cesárea electiva repetida. En 26 pacientes que recibieron 0,1 mg kg^{-1} de pancuronio solemente, se detectó pancuronio en todas las muestras arteriales o venosas umbilicales (0,12 $\mu g\ ml^{-1}$). En 23 pacientes adicionales que recibieron suxametonio en 1,0 mg kg^{-1}, seguido por 0,05 mg kg^{-1} de pancuronio, se detectó pancuronio en la sangre fetal 2 min después de la inyección; la concentración de pancuronio en las muestras arteriales o venosas umbilicales era de 0,08 $\mu g\ ml^{-1}$ en 14 pacientes y menor de 0,05 $\mu g\ ml^{-1}$ en nueve pacientes. No había ninguna prueba de que tales concentraciones de pancuronio perjudicaban al feto. El uso de suxametonio antes del pancuronio tuvo por resultado una disminución de la dosis de pancuronio, del tiempo de inducción–parto, y de las concentraciones fetales de pancuronio, y se acompaño de una mejor condición del neonato.

Br. J. Anaesth. (1980), **52**, 537

PLASMA CONCENTRATION AND METABOLISM OF PHENOPERIDINE IN MAN

L. MILNE, N. E. WILLIAMS, T. N. CALVEY, G. R. MURRAY AND K. CHAN

SUMMARY

The plasma concentrations of phenoperidine were measured in five patients during general anaesthesia. The concentration of the drug decreased rapidly between 2 and 40 min and then declined more slowly. Detectable concentrations of phenoperidine were present in plasma for at least 3 h. In the five patients, the distribution half-life of the drug ranged from 3.19 to 14.23 min and the elimination half-life from 47.31 to 162.30 min. Unchanged phenoperidine and two identified metabolites (pethidine and norpethidine) were present in urine.

Phenoperidine may be used during the maintenance of general anaesthesia and may contribute to postoperative analgesia following surgical procedures. In addition, it is useful in intensive care units in the management of patients requiring prolonged mechanical ventilation. The effects of phenoperidine on respiratory function have been studied previously (Prys-Roberts and Kelman, 1967; Henderson and Parbrook, 1976). Its effects are maximal within 5–15 min, and the duration of action is usually less than 60 min. By contrast, little is known of the plasma concentration, elimination or metabolism of the drug in man. In the present study, we have investigated the clearance of phenoperidine from the circulation after its use as an adjuvant during general anaesthesia, and attempted to isolate the unchanged drug and its principal metabolites from urine.

METHODS

Five patients (three males and two females), who were undergoing e.n.t. or abdominal surgery, were studied. The ages ranged from 22 to 24 yr and the body weights from 65.3 to 80.7 kg. None had clinical or biochemical evidence of anaemia, hepatic or renal disease and none was receiving current systemic drug therapy.

All the patients were premedicated with nitrazepam 10 mg orally (given on the previous night) and diazepam 5–10 mg orally (given on the day of operation). Following the induction of anaesthesia with thiopentone 250–400 mg, either tubocurarine 40–45 mg or pancuronium 7–9 mg was administered. After tracheal intubation, anaesthesia was maintained with nitrous oxide 60–70% and halothane 0.5% in oxygen. Ventilation was controlled. Halothane was discontinued 10–15 min later and droperidol 5–10 mg administered. The duration of surgery was usually 60–90 min and there was little or no fluid loss or replacement. At the end of the operation, residual neuromuscular block was antagonized (neostigmine 5.0 mg and atropine 1.2 mg i.v.). Morphine sulphate 10 mg i.m. was used routinely for analgesia after surgery.

During surgery, an i.v. cannula was placed in a superficial vein and patency maintained by the intermittent infusion of small volumes of saline. Phenoperidine 2.0 mg was injected i.v. into a different vein and blood samples were withdrawn from the cannula after 2, 3, 4, 5, 7, 10, 15, 20, 40, 60, 80, 100, 120, 180 and 240 min, and placed in tubes containing lithium heparin. As soon as possible, plasma was obtained by centrifugation and stored at −20 °C. Collections of urine were made from 0 to 24 h and from 24 to 48 h following injection of the phenoperidine.

Unchanged phenoperidine was extracted from samples of plasma, and the concentration of the drug was determined by gas–liquid chromatography using a nitrogen detector. Phenoperidine and its basic metabolites were extracted from urine in alkaline conditions into a mixture of diethyl ether and dichloromethane (4 : 1, v/v); the concentrated extracts were resolved by thin layer chromatography on silica gel plates. After resolution, spots with R_F values corresponding to phenoperidine and its

---

L. MILNE, M.B., CH.B., F.F.A.R.C.S.; N. E. WILLIAMS, M.B., CH.B., F.F.A.R.C.S.; T. N. CALVEY, B.SC., M.D., PH.D.; Whiston Hospital, Prescot, Lancashire and Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3BX. G. R. MURRAY, B.SC.; K. CHAN, B.PHARM., M.SC., PH.D., M.P.S.; School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF.

Reprint requests to N.W., Whiston Hospital.

0007-0912/80/050537-04 $01.00

© Macmillan Journals Ltd 1980

presumptive metabolites were eluted and analysed by gas–liquid chromatography (Chan, Murray and Calvey, 1979).

RESULTS

In the five patients studied, significant concentrations of phenoperidine (usually greater than 1 ng ml^{-1}) were detected in plasma for 2–3 h after the i.v. administration of the drug (2.0 mg). The plasma concentration of phenoperidine decreased from 21.2 ± 6.5 ng ml^{-1} to 4.6 ± 1.0 ng ml^{-1} (mean ± SEM) between 2 and 40 min, and then declined more slowly (fig. 1). During the first 5 min there were large variations in the concentration of phenoperidine in plasma between subjects, although marked inter-individual differences were not observed subsequently (fig. 1).

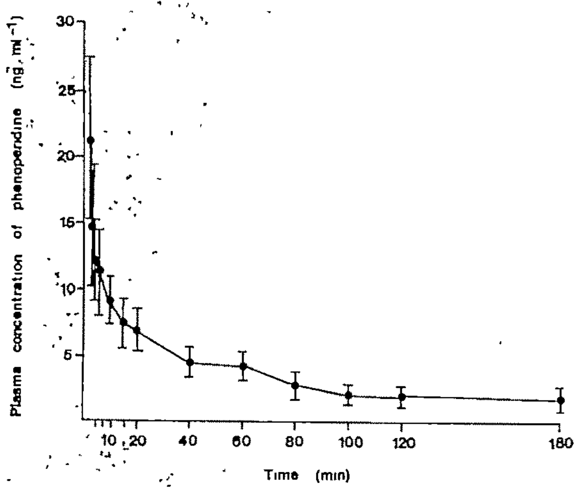


FIG. 1. Plasma concentration of phenoperidine after i.v. injection. Each point and vertical bar represents the mean and standard error of five observations.

The decrease in the plasma concentration of unchanged phenoperidine with time was resolved into both two and three exponential components, using a computer program. In three patients, the experimental data were best expressed as a tri-exponential equation (as assessed by the sum of the squared deviations between the experimental and the computer-derived points); in the other two patients, a bi-exponential solution was more appropriate. In all five patients, the differences between the bi-exponential and tri-exponential solutions were not significant statistically. In consequence, the decline in the plasma concentration of phenoperidine with time was expressed as a bi-exponential equation of the form:

$$C_P = A\,e^{-\alpha t} + B\,e^{-\beta t}$$

where C_P is the concentration of phenoperidine in plasma at time t, and A, B, α and β are constants (table I). Values for the distribution and elimination half-lives were calculated from the expressions:

$$\text{distribution half-life} = 0.693/\alpha$$

$$\text{elimination half-life} = 0.693/\beta$$

In the five patients, the distribution half-life of phenoperidine ranged from 3.19 to 14.23 min, and the elimination half-life from 47.31 to 162.30 min (table II).

TABLE I. *Relation between the plasma concentration of phenoperidine and time. Plasma concentration at time t: $C_P = A\,e^{-\alpha t} + B\,e^{-\beta t}$, where A, B, α and β are constants. * In patient 1, the initial component could not be reliably determined because of technical difficulties*

Patient	Plasma concn of phenoperidine (ng ml^{-1}) at time t
1	* $+9.959e^{-0.015t}$
2	$8.070e^{-0.128t}+6.809e^{-0.012t}$
3	$3.222e^{-0.049t}+0.429e^{-0.004t}$
4	$14.866e^{-0.127t}+9.862e^{-0.008t}$
5	$35.621e^{-0.218t}+6.249e^{-0.009t}$

TABLE II. *Distribution and elimination half-lives of phenoperidine after i.v. injection*

Patient	Distribution half-life (min)	Elimination half-life (min)
1	—	47.31
2	5.50	57.65
3	14.23	162.30
4	5.47	106.73
5	3.19	78.04

Thin layer chromatograms of extracts of urine showed the presence of seven spots. Three of these spots have R_F values corresponding to unchanged phenoperidine, pethidine and norpethidine and gas–liquid chromatographic data indicate that these spots have retention times identical to the authentic compounds. The identity of the remaining spots is unknown.

DISCUSSION

In this study, the decrease in the plasma concentration of phenoperidine after i.v. injection was resolved into two exponential components. The half-life of the initial phase ("distribution half-life") ranged from 3.19 to 14.23 min, and presumably depended mainly on the distribution of phenoperidine in tissues (including the central nervous system). Similar inter-individual differences in the initial half-life were observed after the rapid injection i.v. of other drugs, such as edrophonium and neostigmine, and probably reflect uneven drug distribution in plasma (Calvey et al., 1976; Calvey et al., 1979).

In general, the half-life of the initial phase is consistent with the rate of onset of drug action; maximal respiratory depression usually occurs after 5–15 min (Prys-Roberts and Kelman, 1967). By contrast, the half-life of the terminal phase ("elimination half-life") ranged from 47.31 to 162.30 min and there was a 10-fold difference in the plasma concentration of phenoperidine in the five patients studied. This phenomenon cannot be attributed to variations in drug distribution, and presumably reflects significant individual differences in drug metabolism or excretion. Similar differences are known to occur with numerous other drugs.

In the present studies in anaesthetized and artificially ventilated patients, no assessment of the pharmacological effects of phenoperidine could be made. Nevertheless, it is considered generally that the action of the drug lasts for 45–60 min, suggesting that plasma concentrations of 5 ng ml^{-1} or more are required to produce any action in man.

Although little is known of the metabolism or elimination of phenoperidine, it has been suggested that the drug is metabolized partially to pethidine (Schnieden, 1966). This was confirmed in the present study; both unchanged phenoperidine and pethidine (and norpethidine) were identified in urine by thin layer chromatography and gas–liquid chromatography. The other four spots may represent diazepam, nitrazepam or other weak bases that were present in the urine extract. We hope to establish the nature of these unknown spots.

ACKNOWLEDGEMENTS

The financial assistance of the Mersey Regional Health Authority, the Mason Medical Research Foundation, the Peel Medical Research Trust and Janssen Pharmaceutical Ltd is gratefully acknowledged.

REFERENCES

Calvey, T. N., Wareing, M., Williams, N. E., and Chan, K. (1979). Pharmacokinetics and pharmacological effects of neostigmine in man. *Br. J. Clin. Pharmacol.*, **7**, 149.

—— Williams, N. E., Muir, K. T., and Barber, H. E. (1976). Plasma concentration of edrophonium in man *Clin. Pharmacol. Ther.*, **19**, 813.

Chan, K., Murray, G. R., and Calvey, T. N. (1979). Chromatographic determination and separation of some potent 4-phenylpiperidine narcotics and their metabolites in human biofluids; in *Proceedings of the 2nd World Chromatography Conference* (ed. V. M. Bhatnagar). New York: Marcel Dekker.

Henderson, J. J., and Parbrook, G. D. (1976). Influence of anaesthetic technique on postoperative pain. *Br. J. Anaesth.*, **48**, 587.

Prys-Roberts, C., and Kelman, G. R. (1967). The influence of drugs used in neuroleptanalgesia on cardiovascular and ventilatory function. *Br. J. Anaesth.*, **39**, 134.

Schnieden, H. (1966). A new lytic cocktail. *Prescribers J.*, **6**, 82.

CONCENTRATIONS DE PHENOPERIDINE DANS LE PLASMA ET METABOLISME DE LA PHENOPERIDINE CHEZ L'HOMME

RESUME

On a mesuré les concentrations de phénopéridine dans le plasma de cinq malades au cours de leur anesthésie générale. La concentration du médicament a diminué rapidement entre 2 min et 40 min, mais elle a baissé plus lentement par la suite. Des concentrations de phénopéridine ont été décelées dans le plasma pendant au moins 3 h. Sur les cinq malades, la demi-vie de répartition du médicament s'est échelonnée entre 3,19 et 14,23 min, et la demi-vie d'élimination entre 47,31 et 162,30 min. La phénopéridine intacte, ainsi que deux métabolites identifiés (péthidine et norpéthidine) étaient présents dans l'urine.

PLASMAKONZENTRATIONEN UND METABOLIE VON PHENOPERIDIN BEIM MENSCHEN

ZUSAMMENFASSUNG

Die Plasmakonzentrationen von Phenoperidin wurden bei 5 Patienten während allgemeiner Narkose gemessen. Die Konzentration sank rapide zwischen 2 und 40 min, dann war der Abstieg langsamer. Erkennbare Konzentrationen der Droge hielten sich im Plasma auf mindestens 3 Stunden. Bei den funf Patienten bewegte sich die Verteilungs-Halbwertszeit der Droge zwischen 3,18 und 14,23 min, und die Ausscheidungs-Halbwertszeit zwischen 47,31 und 162,30 min. Im Harn wurden unverändertes Phenoperidin und zwei identifizierte Metaboliten (Pethidin und Norpethidin) festgestellt.

CONCENTRACIONES EN EL PLASMA Y METABOLISMO DE LA FENOPERIDINA EN EL HOMBRE

SUMARIO

Se llévaron a cabo mediciones de las concentraciones de fenoperidina en el plasma de cinco pacientes en el curso de la anestesia general. La concentración de la substancia

bajó rápidamente entre 2 y 40 min y después bajó más lentamente. Se encontraron concentraciones perceptibles de fenoperidina en el plasma durante 3 h por lo menos. En los cinco pacientes, la media vida de repartición de la substancia variaba entre 3,19 y 14,23 min y la media vida de eliminación entre 47,32 y 162,30 min. Se hallaron en la orina fenoperidina no modificada y dos metabolitos identificados (petidina y norpetidina).

Br. J. Anaesth. (1980), **52**, 541

PROLONGED INFUSION OF CHLORMETHIAZOLE IN INTENSIVE CARE

D. B. SCOTT, D. BEAMISH, I. N. HUDSON AND K.-G. JOSTELL

SUMMARY

Chlormethiazole has proved useful for prolonged sedation in patients receiving artificial ventilation of the lungs during intensive care. In short-term infusions sedation and unconsciousness can be produced quickly and reversal is rapid on stopping the administration. After prolonged infusion, however, recovery is much slower because of accumulation of the drug. The pharmacokinetics of chlormethiazole in both short and prolonged infusions were studied in four patients. Following brief administrations the drug disappeared very quickly from the blood as a result of re-distribution and the patients wakened after a few minutes. Unconsciousness was associated with plasma concentrations in the range of 3–5 μg ml^{-1}. After 48 h administration, recovery was much slower, the elimination half-life varying from 3.5 to 12.1 h.

Chlormethiazole is a sedative drug widely used in delirium tremens (Glatt, George and Frisch, 1965) and to a lesser extent in pre-eclampsia (Moir, Victor-Rodrigues and Willocks, 1972). Given i.v. it can cause deep sedation and unconsciousness very rapidly. On stopping the administration, recovery is rapid also (Gabrielsson, Halldin and Palmer, 1961). Thus it is possible to infuse the drug i.v. in such a way as to produce prolonged sedation or even anaesthesia in a controlled way, recovery being rapid once the infusion is stopped. This method has proved useful on many occasions in sedating patients in our intensive care unit during their first hours or days of artificial ventilation.

It has been observed, however, that after infusions lasting 24–48 h, recovery after discontinuing the infusion becomes progressively delayed, as one might expect from a drug which accumulates in the body. To observe the pharmacokinetic behaviour of the drug, plasma concentrations were measured in patients receiving the drug both acutely and by prolonged (48-h) infusion.

METHODS

Four male patients were studied. All were suffering from chest trauma requiring artificial ventilation. Although the trauma was not confined to the thorax, none suffered from head injury requiring frequent assessment of the conscious level and they were thus considered suitable for deep sedation.

Initially, chlormethiazole ethane disulphonate 0.8% was infused at a rate of 8 ml min^{-1} for 5 min (320 mg). (Chlormethiazole ethane disulphonate 1 g $\equiv$ chlormethiazole (base) 0.63 g.) This produced unconsciousness in all patients within 2–4 min. After 5 min the infusion was stopped and the patient allowed to recover consciousness. The time at which the eyes could be opened on verbal command was noted and serial arterial blood samples were taken at 2, 4, 6, 8, 10, 15 and 20 min after starting the infusion. (All patients had an indwelling arterial cannula for routine monitoring.)

After taking the 20-min specimen, the infusion was restarted at a rate of 2 ml min^{-1} (three patients) and 1.5 ml min^{-1} (one patient). Further samples were taken 1, 2, 3, 4, 5, 6, 9, 12, 24, 36 and 48 h after starting the second infusion (except in one patient from whom no sample was taken during the first 24 h). Because of the vagaries of i.v. infusions and the exigencies of the intensive care unit, it was not possible to keep the rate of administration exactly to the amount prescribed, and the patients received 21.4, 27.7, 20.1 and 12.6 g of chlormethiazole (base) respectively in the 48 h. The administration was then stopped and arterial sampling continued for a further 24 h. In one case, sampling was stopped after 6 h because it was necessary to re-sedate the patient with chlormethiazole.

The blood samples were centrifuged and the plasma frozen until estimations of chlormethiazole concentrations could be made by mass fragmentography (Jostell et al., 1978). All concentrations are expressed as chlormethiazole (base). The accuracy of the method is ± 1 ng ml^{-1}.

D. B. SCOTT, M.D., F.R.C.P.E., F.F.A.R.C.S.; D. BEAMISH, F.F.A.R.C.S.; I. N. HUDSON, F.F.A.R.C.S.; Department of Anaesthetics, Royal Infirmary, Edinburgh. K.-G. JOSTELL, M.PH., Astra Research Laboratories, Sodertalje, Sweden.

0007–0912/80/050541–05 $01.00

© Macmillan Journals Ltd 1980

RESULTS

Clinical results

The initial short infusion caused a rapid onset of sedation and unconsciousness. The patients became unrousable about 2 min after the start of the infusion and started to respond 1–3 min after stopping the infusion.

The prolonged infusion took longer to produce unconsciousness (15–30 min) but, once established, only gross stimulation (such as endotracheal suction) produced any response. As a result they were easily managed with regard to ventilation, suction, passive physiotherapy and positional changes. The only change in vital signs was an increase in heart rate of about 20–40 beat min^{-1}. Arterial pressure, central venous pressure and arterial gas tensions were not apparently affected. There was an increase in mucous secretions in the upper airway, but not in the amount of tracheal secretions as indicated by the results of tracheal suction.

Opiates (usually papaveretum 20 mg i.v.) were given whenever reaction to painful procedures appeared to warrant them.

At the end of the prolonged infusion, recovery of consciousness was slow, taking from 4 to 12 h. One patient became very restless during recovery and was re-sedated with chlormethiazole.

Pharmacodynamics

Initial infusions of 8 ml min^{-1} caused a rapid increase in plasma concentrations, followed by a rapid decrease once the infusion was stopped (fig. 1). The maximum concentrations were approximately 10 µg ml^{-1}. There appeared to be a good correlation between the arterial plasma concentration and the depth of sedation, 3–5 µg ml^{-1} being approximately the concentration associated with unconsciousness.

The prolonged infusion at 2 ml min^{-1} caused a slow increase in plasma concentration; a steady state was reached in about 24 h, the concentration at this time being 10–20 µg ml^{-1}. In one patient (B) the concentration decreased in the second 24 h from 20 to 10 µg ml^{-1} in spite of maintaining the same infusion rate. In another (C) it increased from 5 µg ml^{-1} to 9 µg ml^{-1}, and returned to 5 µg ml^{-1} in the second 24 h, again during a constant rate infusion.

On discontinuation of the infusion, the plasma concentration decreased only very slowly, although in one case (D) there was an initial decrease from 10 to 8 µg ml^{-1} (fig. 2) over 20 min.

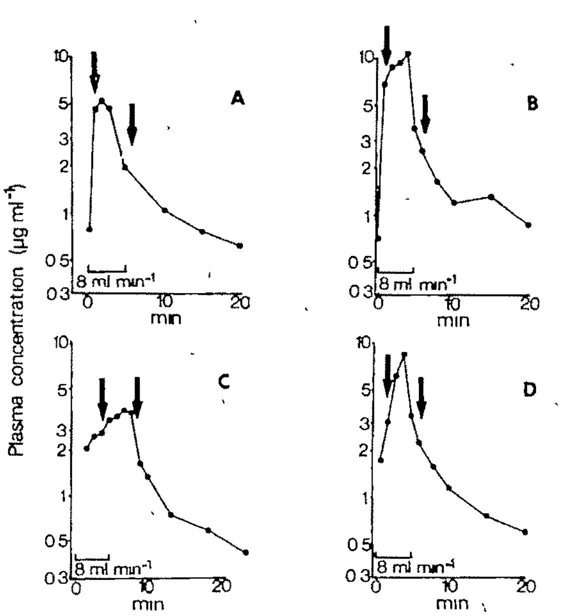


FIG. 1. Plasma concentrations (log scale) of chlormethiazole (base) in four patients during and following chlormethiazole ethane disulphonate 320 mg infused over 5 min. Arrows represent the times at which the patients lost and regained consciousness.

Again, the decrease in arterial plasma concentrations was reflected in the speed of recovery of consciousness.

The pharmacokinetic calculations are shown in table I. They indicate that after the very large doses of chlormethiazole used in these patients the clearance of the drug is rather slow, varying from 0.44 to 0.78 (mean 0.62) litre of plasma per minute. The elimination half-life ($T_{\frac{1}{2}}\beta$) varied from 3.5 to 12.1 (mean 7.9) h. In this regard the shortest half-life occurred in the youngest patient (17 yr old) and the longest was in an older (57 yr old) and more seriously ill patient. The volume of distribution (V^{β}) varied from 221 to 571 (mean 402) litre.

It is realized that in patient A, in whom plasma concentration was not determined in the first 24 h of infusion, AUC had to be estimated by backward extrapolation of the plasma concentration curve. Any error in doing this was thought to be small in relation to total AUC.

DISCUSSION

For many years chlormethiazole has been used with success while establishing artificial ventilation in

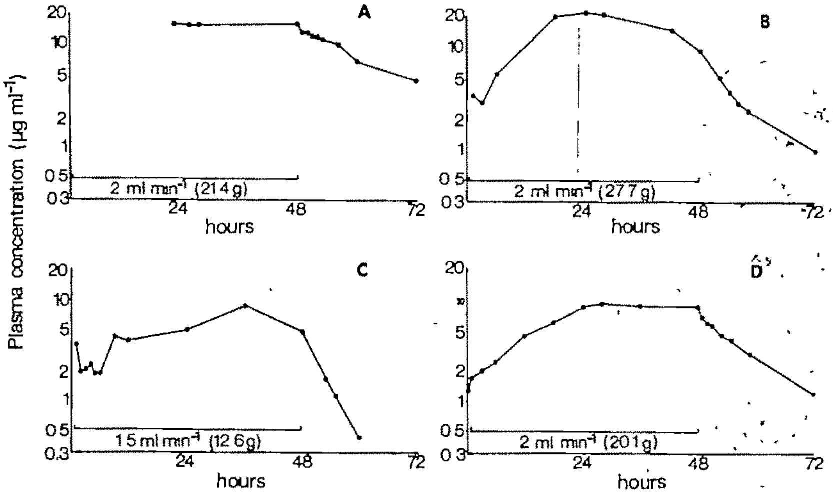


FIG. 2. Plasma concentrations (log scale) of chlormethiazole in four patients during and following continuous infusion for 48 h. (Plasma samples were not obtained from patient A during the first 24 h.) Total doses are given as chlormethiazole (base).

TABLE I. *Pharmacokinetic data in four patients receiving chlormethiazole i.v. for 48 h. AUC = area under concentration curve. $\dot{V}$ = clearance of drug, $T_{\frac{1}{2}}\beta$ = half-life of elimination phase, V^{β} = volume of distribution*

	Patient				
	A	B	C	D	Mean
Age (yr)	57	36	17	61	42.7
Weight (kg)	60	84	64	83	73
Total dose (mg base)	21 410	27 700	12 590	20 150	20 463
AUC (mg h^{-1} litre^{-1})	820.1	829.4	288.1	432.7	592.6
$\dot{V}$ (litre min^{-1})	0.44	0.56	0.73	0.78	0.62
(ml min^{-1} kg^{-1})	7.3	6.6	11.4	9.4	8.7
$T_{\frac{1}{2}}\beta$ (h)	12.1	7.5	3.5	8.5	7.9
V^{β} (litre)	456	361	221	571	402
(litre kg^{-1})	7.6	4.3	3.5	6.9	5.6

patients in this hospital. The only side-effects of note are tachycardia and increase in mucous secretions in the upper airway.

Chlormethiazole produces rapid sedation which can be deep enough to be classified as anaesthesia. Analgesia does not appear to be a marked feature (Dundee, 1958) and opiates have to be given frequently. Recovery from sedation is initially very rapid, allowing good control with an i.v. infusion. The more prolonged the infusion, however, the longer the recovery. The pharmacokinetic behaviour of the drug explains these characteristics.

In the four patients studied, clearance was generally less than in previously reported series (table II). This may have resulted from the poorer physical condition of our patients, who were all undergoing intensive care.

Previous reports giving results from healthy volunteers showed clearances considerably greater than those seen in our patients. However, in two series, one consisting of old volunteers (mean age 73 yr) (Nation et al., 1976) and one consisting of patients with cirrhosis of the liver (Pentikäinen et al., 1978), the clearance rates were only marginally greater than

TABLE II. *Mean pharmacokinetic data in four intensive care patients receiving i.v. chlormethiazole for 48 h compared with previous published results (Moore et al., 1975; Nation et al., 1976; Jostell et al., 1978; Pentikainen et al., 1978) in volunteers and patients receiving brief i.v. infusions. The data from Jostell and others have been re-calculated to correspond to plasma concentrations instead of whole blood, using a blood/plasma ratio of* 0.76

	Scott: Intensive care	Jostell: Young normal	Moore: Young normal	Nation: Old normal	Pentikäinen: Middle aged	
					Normal	Cirrhosis
Dose (mg base)	20 463	192.0	756	756	192	192
AUC ($mg\ h^{-1}\ litre^{-1}$)	592.6	1.47	9.57	14.4	2.48	3.73
V_B ($litre\ min^{-1}$)	0.62	3.76	1.52	0.87	1.29	0.85
($ml\ min^{-1}\ kg^{-1}$)	8.7	64.5	22.97	14.0	18.1	12.8
$T_{\frac{1}{2}}\ \beta$ (h)	7.9	3.7	4.1	8.49	6.6	8.7
V^{β} (litre)	402	1320	506.7	694.4	737	640
($litre\ kg^{-1}$)	5.6	20.6	7.7	11.2	10.2	9.8

ours. It is tempting to implicate the hepatic blood flow as the principal factor in the decreased clearance, and variations in this flow could explain the variations in plasma concentrations seen in two patients during the second 24 h of constant infusion. The difficulty in maintaining an exact rate of infusion has been mentioned, but any variation that occurred is unlikely to have caused the large changes seen in these two patients. It is postulated that, as the patient's circulation improved in response to treatment, his liver blood flow, and thus blood clearance, increased.

The volumes of distribution in our patients were also less than previously reported (table II) possibly because blood flow throughout the body was of an altered pattern compared with the normal.

Chlormethiazole has a very large distribution space such that, initially, there is a rapid decrease in plasma concentrations once the infusion is stopped and the drug leaves the vascular compartment. Once the distribution space has been saturated, however, the drug can only leave the vascular space as a result of metabolism which occurs almost entirely in the liver. Thus, variations in liver blood flow and liver function may be highly relevant to the speed of recovery after prolonged infusions. It was noted in one of our patients that the plasma concentration decreased during the second 24 h of the constant infusion. This can be explained by an increase in liver blood flow, presumably as a result of improvement in the patient's cardiovascular condition.

The concentration of chlormethiazole in arterial blood necessary to cause unconsciousness is of the order of 3–5 $\mu g\ ml^{-1}$, although this will of course be affected by the concomitant use of other sedative drugs.

Chlormethiazole has been used as an anaesthetic agent with variable success, and its lack of effect on the cardiovascular system (Wilson, Stephen and Scott, 1969) and the rapid recovery associated with stopping the administration are of advantage. In prolonged sedation it is extremely useful in the management of seriously ill patients requiring artificial ventilation, provided the following points are borne in mind:

(1) Recovery of consciousness will become progressively delayed with increasing duration of administration. To avoid unnecessarily great plasma concentrations it is advisable to discontinue the administration every few hours to allow some lightening of the sedation.

(2) Chlormethiazole is not an analgesic and opiates should be given as required.

(3) An increase in upper airway (nose and pharyngeal) secretions can occur and requires suction. No increase in tracheo-bronchial secretions has been noticed.

(4) Tachycardia is common.

(5) As solutions more concentrated than 0.8% cause thrombophlebitis and are not available, the dangers of water overload should be remembered. Adequate maintenance of serum electrolyte concentrations can be achieved by adding appropriate amounts of sodium and potassium chloride to the solutions.

(6) Thrombosis of the vein used for infusion is not uncommon with chlormethiazole and the use of a large central vein is recommended.

(7) Haemolysis of erythrocytes can occur if chlormethiazole concentrations greater than 0.8% are infused (Jörgenson, 1963).

REFERENCES

Dundee, J. W. (1958). S.C.T.Z.—a new intravenous anaesthetic? *Br. J. Anaesth.*, **30**, 409.

Gabrielsson, G., Halldin, M., and Palmer, B. (1961). Heminevrin in intravenous anaesthesia. *Opusc. Med. (Stockh.)*, **4**, 2.

Glatt, M. M., George, H. R., and Frisch, E. P. (1965). Controlled trial of chlormethiazole in treatment of the alcoholic withdrawal phase. *Br. Med. J.*, **2**, 401.

Jörgensen, H. (1963). Heminevrin till intravenös narkos. Ett material omfattande collumfrakturer. *Svenska Läk.-Tidn.*, **60**, 319.

Jostell, K.-G., Agurell, S., Allgen, L.-G., Kuylenstierna, B., Lindgren, J.-E., Aberg, G., and Österlof, G. (1978). Pharmacokinetics of chloromethiazole in healthy adults. *Acta Pharmacol. Toxicol.*, **43**, 180.

Moir, D. D., Victor-Rodrigues, L., and Willocks, J. (1972). Epidural analgesia in labour in patients with pre-eclamptic toxaemia. *J. Obstet. Gynaecol.*, **79**, 465.

Moore, R. G., Triggs, E. J., Shanks, C. A., and Thomas, J. (1975). Pharmacokinetics of chlormethiazole in humans. *Eur. J. Clin. Pharmacol.*, **8**, 353.

Nation, R. L., Learoyd, B., Barber, J., and Triggs, E. J. (1976). The pharmacokinetics of chlormethiazole following intravenous administration in the aged. *Eur. J. Clin. Pharmacol.*, **10**, 407.

Pentikäinen, P. J., Neuvonen, P. J., Tarpila, S., and Syvälahti, E. (1978). Effects of cirrhosis of the liver on the pharmacokinetics of chlormethiazole. *Br. Med. J.*, **2**, 861.

Wilson, J., Stephen, G. W., and Scott, D. B. (1969). A study of the cardiovascular effects of chlormethiazole. *Br. J. Anaesth.*, **41**, 840.

INFUSION PROLONGEE DE CHLORMETHIAZOLE LORS DE SOINS INTENSIFS

RESUME

Le chlorméthiazole s'est révélé être un produit utile pour obtenir la sédation prolongée de malades soumis à une ventilation artificielle des poumons au cours de soins intensifs. Avec les infusions à court terme, on peut obtenir rapidement perte de conscience et sédation, et il est possible d'en inverser aussi rapidement les effets en arrêtant l'administration du produit. Toutefois, après une administration prolongée, la reprise de conscience est beaucoup plus lente du fait de l'accumulation du produit. On a étudié sur quatre malades la pharmacoinétique du chlorméthiazole, aussi bien en infusions courtes qu'en infusions prolongées. Après les administrations de courte duree, le médicament a disparu rapidement du sang du fait de sa redistribution et les malades se sont réveillés quelques minutes plus tard. La perte de conscience a été liée aux concentrations de produit dans le plasma de l'ordre de 3–5 $\mu g\ ml^{-1}$. Après quarante-huit heures d'administration, la reprise de conscience a été beaucoup plus lente, la période d'élimination variant entre 3,5 et 12,1 h.

LÄNGERE INFUSION VON CHLORMETHIAZOL IN DER INTENSIVPFLEGE

ZUSAMMENFASSUNG

Chlormethiazol hat sich als nützliches Mittel für längere Beruhigung von Patienten erwiesen, die während Intensivpflege künstliche Belüftung erhalten. Bei kurzfristigen Infusionen können Beruhigung und Bewusstlosigkeit schnell erzielt werden, und mit Beendigung der Verabreichung auch sehr schnell wieder aufgehoben werden. Nach längerer Infusion dauert die Erholung wesentlich länger, weil die Droge akkumuliert wird. Die pharmakokinetischen Eigenschaften der Droge sowohl bei kurzen als auch bei längeren Infusionen wurden bei 4 Patienten studiert. Nach kurzfristigen Verbreichungen verschwand die Droge rasch aus dem Blut als Ergebnis der Aufteilung, und die Patienten erwachten nach wenigen Minuten. Bewusstlosigkeit stand in Verbindung mit Plasmakonzentrationen zwischen 3 und 5 $\mu g\ ml^{-1}$. Nach 48 Stunden der Verabreichung war die Erholung wesentlich langsamer, und die Ausscheidungs-Halbwertszeit variierte von 3,5–12,1 Stunden.

INFUSION PROLONGADA DE CLORMETIAZOL EN CUIDADOS INTENSIVOS

SUMARIO

Comprobó ser útil el clormetiazol para sedación prolongada de pacientes que recibían una ventilación artificial de los pulmones durante cuidados intensivos. A corto tiempo, se logra rápidamente una sedación y la pérdida de conocimiento en las infusiones y la invesión es rápida cuando se acaba la administración. Sin embargo, después de una infusión prolongada, la recuperación es mucho más lenta por causa de la acumulación de la substancia. Se estudió la farmacocinética del clormetiazol tanto en infusiones a corto tiempo como en infusiones prolongadas en cuatro pacientes. Después de administraciones breves, la substancia desapareció muy rápidamente de la sangre como consecuencia de la redistribución y los pacientes volvieron en sí después de pocos minutos. La pérdida de conocimiento fue asociada a concentraciones en el plasma del orden de 3–5 $\mu g\ ml^{-1}$. Después de una administración de 48 h la recuperación fue mucho más lenta, la media vida de eliminación variaba entre 3,5 y 12,1 h.

Br. J. Anaesth. (1980), **52**, 547

A NEW NERVE STIMULATOR (MYOTEST)

J. VIBY-MOGENSEN, P. H. HANSEN, B. C. JØRGENSEN, H. ØRDING, T. KANN AND B. FRIES

SUMMARY

The Myotest is a new nerve stimulator which can give train-of-four, single twitch (1 and 10 s) and tetanic stimuli. Power is supplied by standard batteries, which allow 200 h effective use. The impulse is unipolar constant current, and the amplitude can be adjusted between 0 and 40 mA. These factors, plus the electronic control of stimulus administration, make the nerve stimulator easy to use, and facilitate the interpretation of responses, especially to tetanic and post-tetanic stimulation.

Routine monitoring of neuromuscular function during and after anaesthesia using nerve stimulators is rare. However, our studies of the frequency of residual curarization in recovery wards (Viby-Mogensen, Jørgensen and Ørding, 1979) have convinced us that there are good reasons to pursue this technique. Probably, one reason why acceptance has been slow despite arguments for the routine use of nerve stimulators (Borden, Clarke and Katz, 1974; Lee, 1975, 1976; Savarese et al., 1975; Ali and Savarese, 1976; Geha, Blitt and Moon, 1976) is that there have been difficulties in the interpretation of the responses to conventional methods of stimulation. The introduction of train-of-four nerve stimulation (Ali, Utting and Gray, 1970, 1971a, b), however, eliminated many of these difficulties.

This report presents a new nerve stimulator (Myotest, figs 2 and 3) which in addition to the traditional stimulation forms—twitch and tetanus—offers train-of-four stimulation. Certain time constants which facilitate interpretation of responses, particularly to tetanic and post-tetanic stimuli, are built in.

Description

The nerve stimulator (figs 1 and 2) measures 90 × 45 × 165 mm and weighs about 400 g. Practical considerations and patient security dictated that the stimulator should be battery driven (4 × 1.5–V standard alkaline batteries, size AA); each set of batteries has a life of about 200 h. The stimulator gives a unipolar constant current impulse, with an adjustable amplitude from 0 to 40 mA, and with a constant impulse duration of 0.2 ms. Maximum allowable resistance between electrodes is 4000 Ω.

Stimulation forms

TOF (train-of-four) (Ali, Utting and Gray, 1970, 1971a, b) comprising four stimuli given at 0.5-s intervals. The train is repeated each 10 s.

1 *s* (single twitch), frequency 1.0 Hz.

10 *s* (single twitch), frequency 0.1 Hz.

TETANY. When this button is pressed, tetanic stimulation (50 Hz, duration 5 s) begins at the time when the next impulse (dependent on the chosen form of stimulation) is due.

Stimulation frequency

CONT (continuous). The machine stimulates continuously with one of the described forms of stimulation. At this setting the stimulator continues automatically with the pre-selected impulses 3 s after termination of a tetanic stimulus.

STB (standby). No stimuli are given, but previous settings (including LEVEL) are preserved. This ensures maintenance of supramaximal stimulation capacity. STB also functions as the basal setting for use of:

INTM (manual). This setting allows administration of a single stimulus of the selected stimulation form.

BATT. Stimulation control light. The light blinks with each impulse, and this gives visual control of the type of stimulation. When the light ceases to function, batteries should be changed. At this point there is still current for approximately 20 h of stimulation, so that the individual study need not be interrupted.

LEVEL. Continuous regulation of impulse amplitude. The control functions also as the "on–off" switch.

JØRGEN VIBY-MOGENSEN, M.D.; PAUL HOWARDY HANSEN, M.D.; BENT CHRAEMMER JØRGENSEN, M.D.; HELLE ØRDING, M.D.; TORBEN KANN, M.S.E.E.; BERNT FRIES; Department of Anaesthesia, Herlev Hospital, University of Copenhagen, DK 2730 Herlev, Denmark.
Reprint requests to J. V.-M.

0007-0912/80/050547-05 $01.00

© Macmillan Journals Ltd 1980

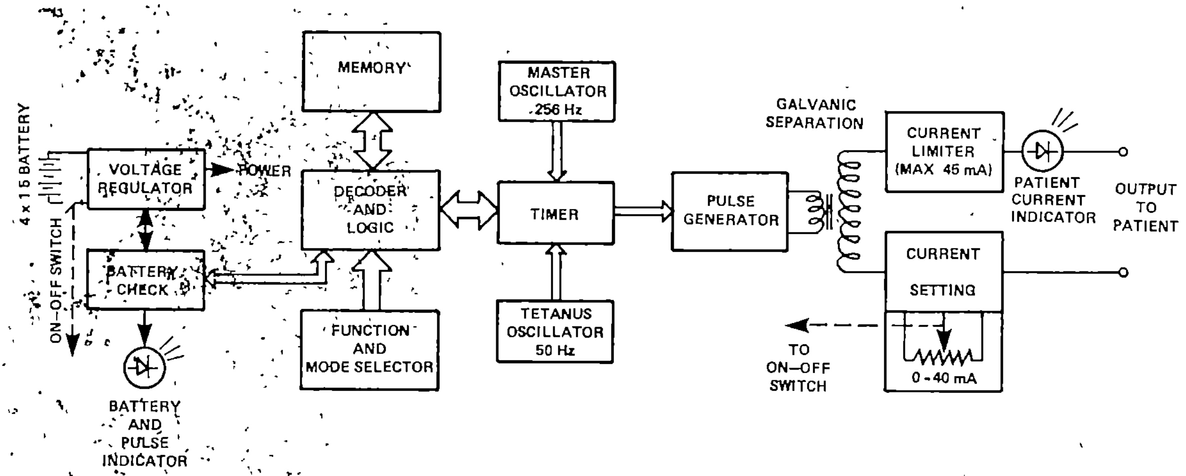


FIG. 1. Block diagram of the stimulator.

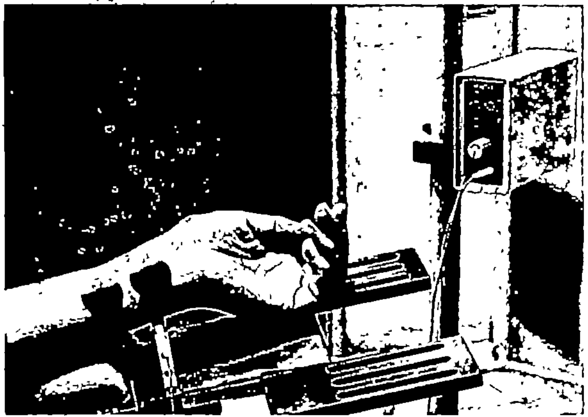


FIG. 2. Myotest nerve stimulator with conductive rubber electrodes.

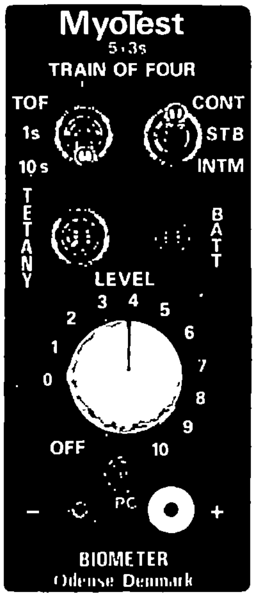


FIG. 3. Front plate of Myotest nerve stimulator.

The connections for the stimulating electrodes are located low on the front plate of the stimulator.

DISCUSSION

The Myotest differs most significantly from other nerve stimulators (Christie and Churchill-Davidson, 1958; Churchill-Davidson, 1965; Katz, 1965; Zeh and Katz, 1978) by giving a unipolar constant current impulse. This means that, irrespective of changes in impedance between the electrodes, the current to the stimulated nerve will be unchanged. This considerably increases the reproducibility of results.

Another advantage is the inbuilt, electronically controlled, time-constant system which facilitates the interpretation of responses, especially to tetanic and post-tetanic stimulation. The response to tetanic stimulation, and the degree of post-tetanic potentiation, is dependent on the frequency of the tetanic stimulus, the duration of that stimulus, and the time lapse between the conclusion of the tetanic stimulus and the first post-tetanic single stimulus. It is therefore of paramount importance that these three variables are held constant, if valid comparison between neuromuscular response to tetanic stimulation at different times during anaesthesia is to be made. When the "tetany" button is pressed, tetanic stimulation follows automatically at the time when the

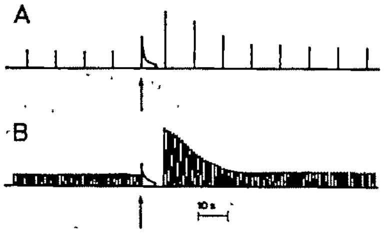


FIG. 4. Twitch, tetanus fade, and post-tetanic potentiation in the presence of a non-depolarizing block. Panel A: thumb twitches at a stimulus rate of 0.1 Hz. Panel B: thumb twitches at a stimulus rate of 1.0 Hz. Arrows indicate tetanic stimulation (50 Hz in 5 s). See text for further explanation.

next stimulus, irrespective of form, would otherwise have been given. (Thus, if the nerve stimulator is programmed to give a single stimulus every 10 s (0.1 Hz), the tetanic stimulus is given 10 s after the previous single twitch response (fig. 4).) The duration of the tetanic stimulus is 5 s and the first post-tetanic twitch stimulation follows 3 s later (fig. 4). This 3-s interval was chosen because the post-tetanic potentiation (decurarization) is maximal at about this time (Wylie and Churchill-Davidson, 1972; authors' unpublished observations).

The choice of a twitch frequency of 0.1 Hz was motivated by the consideration that two successive single stimuli must be separated by about 10 s, if the neuromuscular end-plate is to recover a steady state between stimuli. If this time lapse is not allowed, the response to a given stimulus is decreased initially and constant thereafter, but at a lower amplitude (Ali and Savarese, 1977). A stimulation frequency of 0.1 Hz thus allows the largest possible response to a single stimulus. Despite this, we chose the 1.0-Hz frequency, because we found it useful in our day-to-day use of the stimulator. The 1.0-Hz frequency gives a greater opportunity to elicit the supramaximal intensity at a shorter time and may be used in the initial evaluation of a depolarizing block.

We have used the Myotest nerve stimulator for more than 1 year both in our routine clinical practice and in research projects. It has proved robust, reliable and easy to use.

ACKNOWLEDGEMENT

The Myotest nerve stimulator was constructed by Biometer, Odense, Denmark, in collaboration with the Department of Anaesthesia, Herlev Hospital, University of Copenhagen, Herlev, Denmark.

REFERENCES

Ali, H. H., and Savarese, J. J. (1976). Monitoring of neuromuscular function. *Anesthesiology*, **45**, 216.

—— —— (1977). Stimulus frequency and the dose-response to D-tubocurarine in man. *Abstracts of Scientific Papers*, 1977, ASA Annual Meeting, p. 317.

—— Utting, J. E., and Gray, G. (1970). Stimulus frequency in the detection of neuromuscular block in humans. *Br. J. Anaesth.*, **42**, 967.

—— —— —— (1971a). Quantitative assessment of residual antidepolarizing block (part I). *Br. J. Anaesth.*, **43**, 473.

—— —— —— (1971b). Quantitative assessment of residual antidepolarizing block (part II). *Br. J. Anaesth.*, **43**, 478.

Borden, H., Clarke, M. T., and Katz, H. (1974). The use of pancuronium bromide in patients receiving lithium carbonate. *Can. Anaesth. Soc. J.*, **21**, 79.

Christie, T. H., and Churchill-Davidson, H. C. (1958). The St Thomas's Hospital nerve stimulator in the diagnosis of prolonged apnoea. *Lancet*, **1**, 776.

Churchill-Davidson, H. C. (1965). A portable peripheral nerve stimulator. *Anesthesiology*, **26**, 224.

Geha, D. G., Blitt, C. D., and Moon, B. J. (1976). Prolonged neuromuscular blockade with pancuronium in the presence of acute renal failure. A case report. *Anesth. Analg. (Cleve.)*, **55**, 343.

Katz, R. L. (1965). A nerve stimulator for the continuous monitoring of muscle relaxant action. *Anesthesiology*, **26**, 832.

Lee, C. (1975). Train-of-four quantitation of competitive neuromuscular block. *Anesth. Analg. (Cleve.)*, **54**, 649.

—— (1976). Train-of-four fade and edrophonium antagonism of neuromuscular block by succinylcholine in man. *Anesth. Analg. (Cleve.)*, **55**, 663.

Savarese, J. J., Ali, H. H., Murphy, J. D., Padget, C., Lee, C., and Ponitz, J. (1975). Train-of-four nerve stimulation in the management of prolonged neuromuscular blockade following succinylcholine. *Anesthesiology*, **42**, 106.

Viby-Mogensen, J., Jørgensen, B. C., and Ørding, H. (1979). Train-of-four quantitation of residual neuromuscular blockade in the recovery room. *Anesthesiology*, **50**, 539.

Wylie, W. D., and Churchill-Davidson, H. C. (1972). *A Practice of Anaesthesia*, 3rd edn., p. 823. London: Lloyd-Luke Ltd.

Zeh, D. W., and Katz, R. L. (1978). A new nerve stimulator for monitoring neuromuscular blockade and performing nerve blocks. *Anesth. Analg. (Cleve.)*, **57**, 13.

NOUVEAU STIMULATEUR DE NERFS (MYOTEST)

RESUME

Le Myotest est un nouvel appareil pour la stimulation des nerfs qui peut donner des chaînes de quatre stimulations, des crispations uniques (1 et 10 s) ainsi que des stimulations tétaniques. Le courant est fourni par des piles ordinaires qui permettent 200 h d'utilisation effective. L'impulsion est un courant unipolaire constant et l'amplitude peut être réglée entre 0 et 40 mA. Ces facteurs ajoutés au contrôle électronique de l'administration des stimulations font que

le stimulateur de nerfs est d'un usage simple et qu'il facilite l'interprétation des réactions, particulièrement aux stimulations tétaniques et post-tétaniques.

EIN NEUER NERVENSTIMULATOR (MYOTEST)

ZUSAMMENFASSUNG

Der Myotest ist ein neuer Nervenstimulator, der eine Viererserie von Einzelzuckungs-(1 und 10 s) und tetanischen Stimuli vermitteln kann. Der Antrieb erfolgt durch Standardbatterien, die 200 Stunden lang arbeiten. Der Impuls ist ein einpoliger, knonstanter Strom, und die Amplitude kann zwischen 0 und 40 mA adjustiert werden. Diese Faktoren zusammen mit der elektronischen Regelung der Stimulus-Verabreichung, sorgen fur eine einfache Anwendung des Stimulators und fur eine Erleichterung der Interpretation von Reaktionen, besonders auf tetanische und posttetanische Stimulierung.

NUEVO ESTIMULADOR DE NERVIOS (MIOENSAYO)

SUMARIO

El Mioensayo (*Myotest*) es un nuevo estimulador de nervios que puede procurar una serie de cuatro estímulos, un solo crispamiento (1 y 10 s) y una punzada tetánica. Deriva su energía de baterías normales que permiten un uso durante 200 h. El impulso proviene de una corriente constante unipolar y se puede ajustar la amplitud entre 0 y 40 mA. Estos factores, así como el control electrónico de la administración de los estímulos, hacen del estimulador de nervios un aparato de fácil uso, y facilitan la interpretación de las respuestas, en particular en lo que se refiere a la estimulación tetánica y postetánica.

Br. J. Anaesth. (1980), **52**, 551

EVALUATION OF THE DATEX CD-101 AND GODART CAPNOGRAPH MARK II INFRA-RED CARBON DIOXIDE ANALYSERS

J. P. BLACKBURN AND T. R. WILLIAMS

SUMMARY

Performance of the Datex CD-101 and Godart Capnograph Mark II infra-red carbon dioxide analysers was investigated. The Datex machine uses a solid-state infra-red detector, while the Godart instrument uses a Luft detector. Both instruments were easy to use and the small size and light weight of the Datex was an added convenience. Linearity, stability, response time and the effect of nitrous oxide were within specification in both machines except when 10% carbon dioxide was used with the Datex analyser. Linearity of the Godart instrument was considerably better than 1% full scale deflection (fsd) quoted in the specification, while the Datex analyser was within 2% fsd (4% fsd with 10% carbon dioxide).

The introduction of solid-state detectors for infra-red radiation has made it possible to design a double-beam infra-red carbon dioxide analyser which is compact, light-weight and convenient to use. Infra-red radiation filtered at a wavelength of 4.25 μm passes through a sample chamber and also through a reference chamber containing carbon dioxide-free gas. Carbon dioxide in the sample absorbs infra-red radiation and the two infra-red beams are directed alternately onto a detector. This consists of a small crystal of lithium tantalate, or similar material, which produces a voltage related to the intensity of infra-red radiation. An alternative method for detecting infra-red radiation uses the Luft detector. With this system, the radiation is absorbed by a suitable gas (in this case carbon dioxide) in a closed chamber. As the gas is heated, the pressure in the chamber increases and alterations in pressure are sensed by an electro-manometer (Hill and Stone, 1964; Hill, 1974).

In this paper the performance of the Datex CD-101 solid state detector carbon dioxide analyser (fig. 1) has been evaluated and compared with the Godart Capnograph Mark II which is an infra-red double beam instrument using a Luft detector (fig. 2).

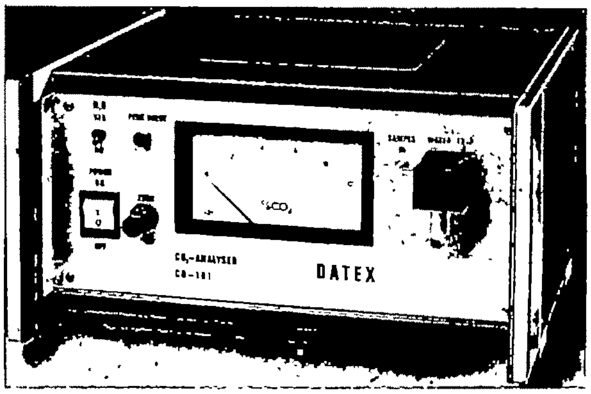


FIG. 1. Datex CD-101 carbon dioxide analyser (courtesy of Vickers Medical).

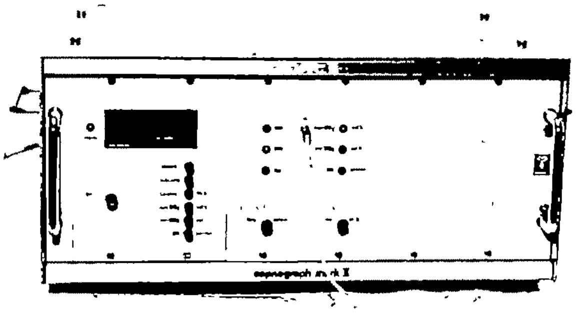


FIG. 2. Godart Capnograph Mark II.

Datex CD-101. The sample can be connected to the inlet directly, or via a water trap if a rapid response is not required. Sample flow rates of 0.4 litre min^{-1} and 1.5 litre min^{-1} are provided. There is a zero control, a preset gain control and a switch to provide compensation for the presence of nitrous oxide. Results are displayed on a meter with linear calibration 0–10% and a push button enables the peak value to be displayed. A recorder output with adjustable gain is provided and a calibration button provides an electrical signal corresponding to 7% carbon dioxide. The weight of the instrument is 8 kg.

J. P. BLACKBURN, F.F.A.R.C.S.; T. R. WILLIAMS, F.F.A.R.C.S.; Department of Clinical Measurement, Westminster Hospital, London S.W.1.

0007–0912/80/050551–05 $01.00

© Macmillan Journals Ltd 1980

Capnograph Mark II. The sample can be connected to the inlet directly or via a water trap. Sample flow rates of 0.1, 0.2 and 0.5 litre min^{-1} can be selected. An "auto zero" push button automatically purges the analyser head with ambient air sampled through a soda-lime cannister and sets the digital display to zero. A "calibrate" button partially occludes the infra-red beam by a filter corresponding to 6% carbon dioxide. In the "autozero" and "calibrate" modes, gas flow through the analyser is reversed and carbon dioxide-free room air, 500 ml min^{-1}, is blown out through the inlet tube. Results are displayed on a digital volt meter with a switch-selectable display of maximum or minimum carbon dioxide concentration, or respiratory rate. Recorder outputs of all signals are provided and a single- or twin-channel recorder can be built into the cabinet. Weight without the recorder is 11 kg.

METHODS

A series of mixtures of carbon dioxide in air and mixtures of carbon dioxide, oxygen and nitrous oxide were prepared, using two Wösthoff gas mixing pumps models 18/3F and 27/3F. The gas mixtures were sampled from a reservoir bag via an inlet tube 100 cm long and 1.5 mm diameter, in such a way that the sampling point was at atmospheric pressure. These gas mixtures were used to assess the linearity of response and the effects of nitrous oxide on the readings. Linearity was investigated by setting zero with carbon dioxide-free air and the gain of the Godart analyser was adjusted with 6% carbon dioxide at 0.1 litre min^{-1} gas flow through the instrument. Gas mixtures containing different concentrations of carbon dioxide were presented in a random order and, at the end of the run, the 6% calibration point was checked once again. With the instrument calibrated at 0.1 litre min^{-1} gas flow, the flow was changed to 0.2 litre min^{-1} and 0.5 litre min^{-1} and readings taken with different gas mixtures as before. The Datex analyser was investigated in a similar manner except that 7% carbon dioxide was used to set the gain and the gas flow through the analyser was 0.4 litre min^{-1}. The response was also investigated at 1.5 litre min^{-1} gas flow.

The effects of nitrous oxide were studied by setting up the analysers using various concentrations of carbon dioxide and oxygen. Nitrous oxide was introduced and the changes in the readings noted.

The stability of the instruments was measured by sampling room air and a standard gas mixture at various times after the instruments had been switched on. The manufacturers recommend that the Godart analyser is left in the "stand by" position continuously. Under these circumstances power is applied to the analyser, but the gas sampling pump is not activated. After a 6-h warm-up period, zero and 5% carbon dioxide gas mixtures were checked at intervals during three 24-h periods. Datex claim that their analyser can be zeroed after being turned on for 1 min and calibrated after a 2-h warm-up period. The zero and gain stability were thus investigated over a period of 2 h.

The response time was investigated by following the change in output when a mixture of 5% carbon dioxide in air was disconnected rapidly from the direct inlet to the analyser or via a 100-cm, 1.5-mm diameter inlet tube. The gas mixture was supplied by a metal tube which fitted loosely over the inlet to the analyser and made electrical contact with it. The sample tube was rapidly disconnected, so that the analyser sampled room air and the electrical connection was broken when the sample tube was removed. This electrical signal was used to trigger an oscilloscope which recorded the change in carbon-dioxide concentration. Measurements were made to the nearest 5 ms, from polaroid photographs taken from the oscilloscope. Overall response time was divided into delay time and 90% response time of the instruments.

Gas flows through the analysers were checked under various conditions using previously calibrated GAP rotameters (Barnes and Birdi, 1977).

The analyser outputs were displayed on a digital volt meter connected to the recorder output sockets.

RESULTS

Linearity for mixtures of oxygen and carbon dioxide is shown in figures 3 and 4. Linear regression equations for the instruments are shown in table I. There were significant differences between the calibration lines for different sample flows in every

TABLE I. *Linear regression equations of actual carbon dioxide concentration v. indicated carbon dioxide concentration*

	Flow (litre min^{-1})	Slope	Intercept	r	SEM
Godart	0.1	0.995	0.031	0.999	0.028
	0.2	0.988	0.032	0.999	0.032
	0.5	0.970	0.044	0.999	0.043
Datex	0.4	0.974	0.040	0.999	0.127
	1.5	0.930	0.033	0.999	0.119

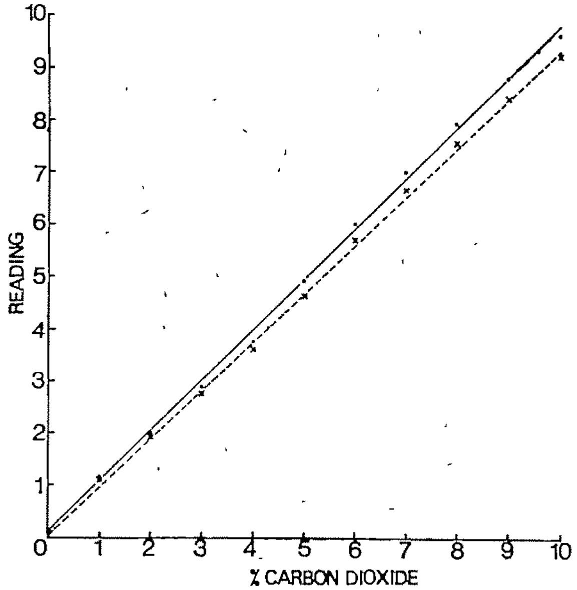


FIG. 3. Linearity of Datex CD-101. ● = sample flow 0.4 litre min^{-1}; × = sample flow 1.5 litre min^{-1}. Analyser calibrated using 0% and 7% carbon dioxide at a sample flow of 0.4 litre min^{-1}.

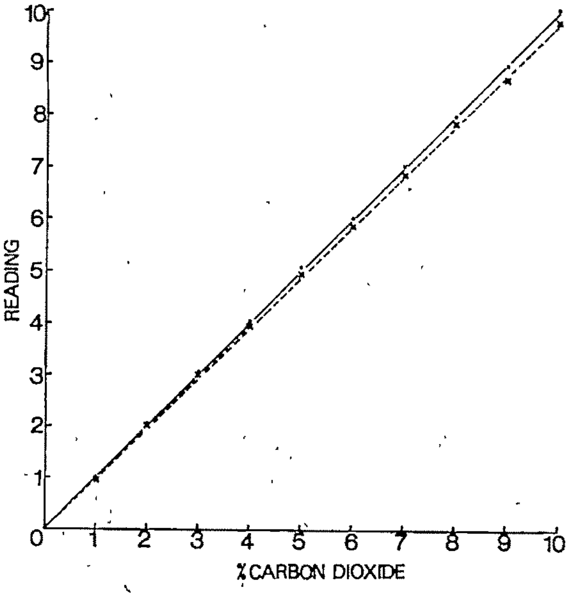


FIG. 4. Linearity of Godart Capnograph Mark II. ● = sample flow 0.1 litre min^{-1}; × = sample flow 0.5 litre min^{-1}. Analyser calibrated using 0% and 6% carbon dioxide at a sample flow of 0.1 litre min^{-1}.

case ($P < 0.005$), although the regression lines for sample flows of 0.1 and 0.2 litre min^{-1} using the Godart analyser are too close to separate in figure 4.

The effects of nitrous oxide are shown in tables II and III. Small concentrations of nitrous oxide are not included in table II (Godart Capnograph), as the readings were within the quoted accuracy of the instrument in the absence of nitrous oxide (change less than 1% full scale deflection (fsd)).

TABLE II. *Effect of nitrous oxide on indicated percentage of carbon dioxide using Godart Capnograph.*

CO_2 (%)	N_2O (%)	Reading of CO_2 (%)	% change when N_2O present
0	100	0.00	0.0
3	97	3.00	0.0
3	68	3.00	0.0
5	95	5.04	0.8
5	67	5.06	1.2
7	93	7.20	2.9
7	65	7.20	2.9
7	47	7.10	1.4

TABLE III. *Effect of nitrous oxide on indicated percentage of carbon dioxide using Datex CD-101*

		Reading of CO_2 (%)		
		N_2O compensation switch		
CO_2 (%)	N_2O (%)	on	off	% change when N_2O present with compensation switch on
0	100	0.04	0.04	
3	97	3.15	3.38	5.0
3	68	3.05	3.28	1.7
3	49	2.97	3.19	−1.0
3	29	2.89	3.10	−3.7
5	95	5.35	5.89	7.0
5	67	5.03	5.57	0.6
5	48	4.86	5.38	−2.8
5	29	4.65	5.15	−7.0
7	93	7.49	8.17	7.0
7	65	7.15	7.80	2.1
7	47	6.86	7.51	−2.0
7	28	6.58	7.22	−6.0

Gas flow at the inlet and outlet of the analysers is shown in table IV. The leak noted in the Datex analyser at high flows occurred between the detector and the pump and did not affect the accuracy of the instrument.

TABLE IV. *Flow rates measured with rotameters attached at the inlet and outlet of the analyser*

	Setting (litre min^{-1})	Reading (litre min^{-1}) Inlet	Reading (litre min^{-1}) Outlet
Godart	0.1	0.09	0.09
	0.2	0.21	0.21
	0.5	0.52	0.52
Datex	0.4	0.41	0.42
	1.5	2.75	3.40

Table V. *Response time, measured to nearest 5 ms, following rapid removal of 5% carbon dioxide from the inlet*

	Flow (litre min^{-1})	Delay time (ms)	90% response time (ms)
Godart			
Direct inlet	0.1	150	195
	0.2	90	120
	0.5	60	85
Sample via 100 cm tube	0.1	1350	300
	0.2	650	215
	0.5	275	135
Datex			
Direct inlet	0.4	105	115
	1.5	20	60
Sample via 100 cm tube	0.4	550	200
	1.5	95	85

Response time is indicated in table V and was measured without the water trap, both directly at the inlet to the analyser and using 100-cm, 1.5-mm diameter inlet tube.

The Godart analyser remained stable during each 24-h test period. Zero and sensitivity drifted by less than 1%. Wide fluctuations in zero and gain were noted after switching on the Datex analyser, but these became stable after 15 min and subsequent drift over the next 105 min was less than 1%.

DISCUSSION

The Godart Capnograph was within its quoted specification in all respects. No cross-sensitivity for nitrous oxide was found and collision broadening, where nitrous oxide alters the reading in the presence of carbon dioxide, was less than 3% of the reading. The autozero facility, where the instrument was automatically purged with carbon dioxide-free air and the display set to zero, was particularly useful, although care should be taken that the analyser is not left in this mode when connected to an anaesthetic circuit, as room air 500 ml min^{-1} is pumped out of the inlet. Accuracy was better than 1% fsd using both internal calibration and known gas mixtures at 0.1 and 0.2 litre min^{-1}. With a 100-cm sample tube and a flow of 0.5 litre min^{-1} a decrease in the reading of up to 3% fsd was found when the analyser was calibrated at slow flows, because the pressure within the analyser was decreased as the flow increased. Gas sampled through the analyser could be returned to an external circuit if necessary.

The Datex CD-101 has a stated accuracy of 2% fsd and this was confirmed except when 10% carbon dioxide was used. The "7% calibration button" provides an electrical output which is useful for setting up a recorder, but does not check the sensitivity of the analyser head. There is no autozero facility. Gas flow through the instrument was reasonably accurate at slow flows (0.4 litre min^{-1}), but was nearly double the indicated setting at fast flows and, furthermore, air-leaks within the instrument beyond the detector resulted in the output from the pump being substantially greater than the flow through the analyser head at the inlet of the instrument.

Cross-sensitivity and collision broadening between nitrous oxide and carbon dioxide were found and a "nitrous oxide" switch introduced an electrical offset which compensated the analyser to within 2% fsd when 50–70% nitrous oxide was present (table III). The instruction manual states that the analyser is "factory calibrated and should be recalibrated if required for use under abnormal conditions". This information is misleading as, under high flow conditions (nominally 1.5 litre min^{-1}), actually 2.75 litre min^{-1}) the pressure in the analyser head is substantially subatmospheric when a 100-cm sample tube is used and errors of up to 8% fsd were found. It is important that the analyser should be calibrated under conditions of use.

The Datex CD-300 has been introduced recently. This instrument was not tested, as the detector system and basic electronics are identical. A chart recorder and switch-selectable digital display of maximum or minimum carbon dioxide concentration, or respiration rate are provided. An additional flow rate of 0.2 litre min^{-1} is also available.

The accuracy of an infra-red carbon dioxide analyser with a Luft detector was investigated by Cormack and Powell (1972). They found that the accuracy of the instrument could be increased from 0.1% to 0.01% if certain precautions were taken. In particular, careful control of room temperature and the pressure within the detector was necessary. They found that changes in barometric pressure during a 3-h period were usually insignificant. Our studies were carried out over a similar period of time and we also observed changes in calibration when the pressure within the detector varied with alterations in gas flow through the instrument.

Solid-state infra-red detectors have been developed for use in various gas analysers, including "in line" instruments using an airway adaptor placed directly in the breathing circuit. They are light, compact and require only a short-period for stabilization. However, in the two instruments tested, the analyser with the conventional Luft detector achieved better performance in all respects.

ACKNOWLEDGEMENTS

The authors wish to thank Vickers Medical and Gould Medical U.K. for the loan of the analysers.

REFERENCES

Barnes, P., and Birdi, H. (1977). An assessment of the gap-meter laboratory kit. *Br. J. Anaesth.*, **49**, 277.

Cormack, R. S., and Powell, J. N. (1972). Improving the performance of the infra-red carbon dioxide meter. *Br. J. Anaesth.*, **44**, 131.

Hill, D. W. (1974). Methods for the analysis of gases and vapours; in *Scientific Foundations of Anaesthesia* (eds C. Scurr and S. A. Feldman). London: Heinemann.

—— Stone, R. N. (1964). A versatile infra-red gas analyser using transistors. *J. Sci. Instrum.*, **41**, 732.

EVALUATION DES ANALYSEURS ELECTRONIQUES DE GAZ CARBONIQUE DATEX CD-101 ET GODART CAPNOGRAPH MARK II

RESUME

On a fait des recherches sur les performances des analyseurs électroniques de gaz carbonique Datex CD-101 et Godart Capnograph Mark II. La machine Datex est basée sur un détecteur électronique à semi-conducteurs, alors que l'instrument Godart est basé sur un détecteur Luft. Les deux instruments sont faciles à utiliser, mais de par sa petite taille et sa légèreté, le Datex est plus maniable. La linéarité, la stabilité, le temps de réaction et les effets du protoxyde d'azote se situent dans les limites des spécifications de chacune des machines, sauf lorsqu'on a utilisé 10% de gaz carbonique avec l'analyseur Datex. La linéarité de l'instrument Godart a été très nettement meilleure que le 1% de déviation maximale indiqué dans les spécifications, alors que celle de l'analyseur Datex s'est située dans les 2% de déviation maximale (4% avec 10% de gaz carbonique).

BEWERTUNG DER INFRAROT-KOHLENDIOXYD-ANALYSATOREN DATEX CD-101 UND GODART CAPNOGRAPH MARK II

ZUSAMMENFASSUNG

Die Leistungen der beiden Geräte wurden untersucht. Die Datex-Maschine verwendet einen Festkörper-Infrarotdetektor, während das Godart-Instrument einen Luft-Detektor verwendet. Beide Geräte waren einfach in der Anwendung, wobei geringes Gewicht und geringe Grösse des Datex ein zusätzlicher Vorteil waren. Linearität, Stabilität, Reaktionszeit und die Auswirkung von Stickoxyd entsprachen den Spezifikationen beider Maschinen, ausser als mit der Datex 10% Kohlendixyd verwendet wurden. Die Linearität des Godart-Instruments war wesentlich besser als die 1%ige Abweichung, die in der Spezifikation angegeben war, während der Datex sich innerhalb der 2%igen Abweichung bewegte (4%ige Abweichung mit 10% Kohlendioxyd).

EVALUACION DE LOS ANALIZADORES A DIOXIDO DE CARBONO INFRAROJO DATEX CD-101 Y CAPNOGRAFO GODART MARK II

SUMARIO

Se llevó a cabo investigaciones sobre la performancia de los analizadores a dióxido de carbono infrarojo Datex CD-101 y Capnógrafo Godart Mark II. Se usa en la máquina Datex un detector infrarojo transistorizado, mientras que en el instrumento Godart, se usa un detector Luft. Ambos instrumentos son de fácil uso y el pequeño tamaño y bajo peso del Datex constituyen una ventaja adicional. La linearidad, la estabilidad, el tiempo de respuesta y el efecto del óxido nitroso se hallaban dentro de las especificaciones en ambas máquinas, salvo cuando se uso dióxido de carbono al 10% en el analizador Datex. La linearidad del instrumento Godart fue mucho mayor que la deflección de escala total (fsd) del 1% indicada en las especificaciones, mientras que el analizador Datex se encontraba dentro de un 2% del fsd (4% fsd con dióxido de carbono al 10%).

Br. J. Anaesth. (1980), **52**, 557

TEMPERATURE ALARM AND CUT-OUT SYSTEM FOR USE WITH HEATED WATER HUMIDIFIERS

P. Whitehurst and D. St Andrew

SUMMARY

The temperature of the inspired humidified gases of an intubated patient may be monitored accurately, close to the airway, by a commercially available thermistor probe and alarm/cut-out device for use with heated water humidifiers. The apparatus is designed to alarm when the inspired gas temperature exceeds the pre-set temperature and when the thermistor probe is in open or short circuit. When the temperature alarm is activated, the humidifier heater is switched off automatically, thus preventing prolonged transmission of excessively hot gases to the airway. The apparatus has been used successfully in this hospital for several months, requiring minimal observer attention and maintenance.

Humidification of the gases inspired via a tracheal tube is accepted as a routine in the intensive care unit and has been advocated for patients receiving general anaesthesia (Boys and Howells, 1972). In many hospitals heated water humidifiers are a relatively cheap, effective way of achieving suitable conditions. Clinical problems associated with these devices include hyperthermia (Kirch and Dekornfeld, 1967) and respiratory burns (Klein and Graves, 1974). To protect the patient in such instances, an instrument has been developed and it is now commercially available (Draeger Medical Limited) (fig. 1).

The instrument is an electronic over-temperature cut-out. A medical grade thermistor probe measures the temperature of the inspired gas at the tracheal or tracheostomy tube and is designed to alarm and prevent this temperature from reaching a dangerous value.

The instrument measures 20 × 15 × 8 cm and displays temperature in the range 10–50 °C. The alarm can be internally pre-set to activate at any temperature from 35 °C to 42 °C, but is normally set at 39 °C. The humidifier heater is plugged into a mains socket which is on the back of the cut-out and controlled by it. When the pre-set alarm temperature has been reached, visual and audible warning is given and at the same time the power to the humidifier is switched off. The power will remain off until it is restored manually. Restoration can be achieved only when the temperature decreases to less than the pre-set value.

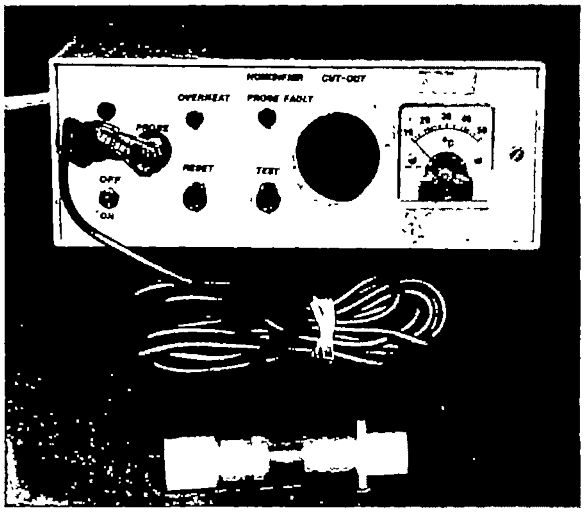


FIG. 1. Alarm and cut-out system with thermistor probe.

The instrument is designed to recognize a faulty probe and carries a "probe fault" indicator light. It has facilities incorporated for calibration and alarm checks. When a TEST button is depressed, the instrument should read 40 °C and the alarm circuit should activate. It is suitable for use with any humidifier of power rating up to 200 VA.

DISCUSSION

British Standard (4494: 1970) states that the temperature at the patient end of the circuit should not exceed 42 °C. Siting the thermistor at the patient end of the circuit ensures that the temperature of the gases delivered to the patient is monitored. This

---

P. Whitehurst, M.B., CH.B.; D. St Andrew, C.ENG.; Anaesthetic Department, University College Hospital, Gower Street, London WC1.

0007–0912/80/050557–02 $01.00

© Macmillan Journals Ltd 1980

helps to avoid over-heating with its associated morbidity, and under-heating with the resultant decrease in humidification. In addition, it will register any increase in temperature occurring distal to the humidifier which, for example, may occur in a paediatric incubator where the delivery pipe crosses heated elements.

ACKNOWLEDGEMENT

The authors wish to thank Mrs S. Beeby for her secretarial assistance.

REFERENCES

Boys, J. E., and Howells, T. H. (1972). Humidification in anaesthesia. *Br. J. Anaesth.*, **44**, 879.

Kirch, T. J., and Dekornfeld, T. J. (1967). An unexpected complication (hyperthermia) while using the Emerson post-operative ventilator. *Anesthesiology*, **28**, 1106.

Klein, E. F., and Graves, S. A. (1974). "Hot pot" tracheitis. *Chest*, **65**, 225.

SYSTEME DE SURVEILLANCE DE LA TEMPERATURE ET COUPE-CIRCUIT A UTILISER AVEC LES HUMIDIFICATEURS A EAU CHAUDE

RESUME

On peut surveiller très précisément la température des gaz humidifiés inspirés par un patient soumis à une intubation, grâce à un appareil que l'on peut se procurer dans le commerce et que l'on place près des passages d'air. Cet appareil comporte une sonde à thermistor ainsi qu'un dispositif alarme/coupe-circuit que l'on peut utiliser avec les humidificateurs à eau chaude. Cet appareil est conçu de façon à donner un signal d'alarme lorsque la température du gaz inspiré est plus élevée que la température préréglée et lorsque la sonde du thermistor est en circuit ouvert ou en court-circuit. Lorsque le signal d'alarme de la température se déclenche, l'appareil de chauffage de l'humidificateur s'arrête automatiquement, ce qui empêche la transmission prolongée de gaz excessivement chauds aux passages d'air. Cet appareil est utilisé par notre hôpital depuis plusieurs mois; il donne toute satisfaction, n'exige qu'un minimum d'attention de la part de l'observateur, et ne requiert qu'un minimum d'entretien.

TEMPERATURALARM UND AUSSCHALTSYSTEM BEI WARMWASSERBEFEUCHTERN

ZUSAMMENFASSUNG

Die Temperatur der von einem intubierten Patienten angesaugten, befeuchteten Gase kann nahe dem Luftweg genau überwacht werden—durch einen kommerziell erhältlichen Thermistor und ein Alarm/Ausschaltgerät zur Verwendung mit Warmwasserbefeuchtern. Der Apparat gibt Alarm, wenn die Temperatur des angesaugten Gases den voreingestellten Wert überschreitet, und wenn sich der Thermistor in einem offenen oder kurzem Stromkreis befindet. Wird der Temperaturalarm ausgelöst, dann schaltet sich der Befeuchtungserhitzer automatisch ab, wodurch eine längere Zuleitung stark überhitzter Gase in den Luftweg verhindert wird. Der Apparat wurde in diesem Krankenhaus mehrere Monate lang erfolgreich verwendet, wobei er minimale Beaufsichtigung und Wartung benötigte.

SISTEMA DE ALARMA Y CORTE DE TEMPERATURA PARA USO CON HUMIDIFICADORES DE AGUA CALENTADA

SUMARIO

Se puede vigilar con exactitud la temperatura de los gases humidificados inspirados de un paciente entubado, cerca de la vía respiratoria, mediante un aparato de alarma/corte y sonda a resistencia térmica disponible en el comercio para su uso con humidificadores de agua calentada. El aparato es diseñado para dar la alarma cuando la temperatura de los gases inspirados excede de la temperatura pre-adjustada y cuando la sonda a resistencia térmica se encuentra en circuito abierto o en corto-circuito. Cuando la alarma de temperatura funciona, el calentador del humidificador se corta automáticamente, impidiendo así la transmisión de gases excesivamente calientes en la vía respiratoria. Se ha usado el aparato con todo éxito en el presente hospital durante varios meses, el que requiere una vigilancia y un mantenimiento mínimos de parte del observador.

Br. J. Anaesth. (1980), **52**, 559

CORRESPONDENCE

REGURGITATION DURING LAPAROSCOPY

Sir,—May I be allowed to comment on the paper of Dr Duffy (1979) on regurgitation during laparoscopy before it is accepted into anaesthetic dogma that all such patients should receive metoclopramide and magnesium trisilicate.

In assessing the risk of Mendelson's syndrome in this operation, it might be wiser to look at the frequency of the syndrome itself rather than extrapolating from the detection of acid in the pharynx. In the series of 50 000 laparoscopies, studied prospectively under the aegis of the Royal College of Obstetricians and Gynaecologists (1978) the frequency of inhalation of gastric contents was zero. In approximately 5000 of these patients the trachea was not intubated. If drugs are to be given to protect against the remote possibility of aspiration, many thousands must be treated to prevent one such case. If metoclopramide and magnesium trisilicate were totally harmless then one might not cavil at the recommendation to give them. Where, however, is the evidence that they are harmless? It is unlikely that any drug can be given to many thousands of patients without some side effects.

In the case of magnesium trisilicate it is often forgotten that the compound is very alkaline and if inhaled will itself cause Mendelson's syndrome. If the stomach is empty (as is the case in most patients undergoing laparoscopy) then no neutralization of this alkali will occur and the patient is as much at risk as if the pH were 2.5 or less.

D. B. Scott
Edinburgh

REFERENCES

Chamberlain, G., and Brown, J. C. (1978) (Eds). *Gynaecological Laparoscopy*. Report of Working Party into Confidential Enquiry by the Royal College of Obstetricians and Gynaecologists.

Duffy, B. C. (1979). Regurgitation during pelvic laparoscopy. *Br. J. Anaesth.*, **51**, 1089.

ANAESTHESIA-INDUCED RHABDOMYOLYSIS IN DUCHENNE MUSCULAR DYSTROPHY

Sir,—Patients with Duchenne muscular dystrophy (DMD) are generally not considered susceptible to anaesthesia-induced malignant hyperthermia and rhabdomyolysis (Richards, 1972). We report the occurrence of this complication in a 5-yr-old boy during adenotomy at a regional hospital. There was no family history of neuromuscular disease or anaesthetic-related complications. After premedication with atropine 0.15 mg and diazepam 1.5 mg, anaesthesia was induced with halothane and nitrous oxide in oxygen, followed by suxamethonium 25 mg. This prompted rigidity of masseter and limb muscles and was followed a few minutes later by cardiac arrest. The patient was successfully resuscitated. Metabolic acidosis (pH 7.13; base excess 20 mmol litre^{-1}) was corrected by i.v. sodium bicarbonate. Rectal temperature increased to 38.5 °C within 30 min. Urine passed subsequently was red and was shown to contain myoglobin. On admission to our hospital 3 h later, there was still marked rigidity predominantly affecting the lower limbs. This was relieved after i.v. dantrolene sodium 100 mg. The urine cleared within 24 h. Creatine phosphokinase (CPK), monitored daily, was 30 000 u. litre^{-1} (normal <80 u. litre^{-1}) on admission and decreased gradually over 1 week to be repeatedly normal 8–12 days later. The clinical findings were characteristic for DMD with waddling gait, positive Gower's manoeuvre and calf hypertrophy. The e.m.g. was consistent with a myopathic process. Quadriceps muscle biopsy, performed under local anaesthesia 3 months later, confirmed muscular dystrophy. CPK at this time was 9300 u. litre^{-1}.

We are aware of only four reports describing seven DMD patients with anaesthesia-induced rhabdomyolysis (Watters, Karpati and Kaplan, 1977; Miller et al., 1978; Reske-Nielsen, 1978; Seay, Ziter and Thompson, 1978). Hyperthermia was mentioned in two of these (Watters, Karpati and Kaplan, 1977; Reske-Nielson, 1978), cardiac arrest in two others (Seay, Ziter and Thompson, 1978). Suxamethonium was administered in all cases, and halothane in all but one (Seay, Ziter and Thompson, 1978). Although the available literature does not allow us to estimate the frequency of these complications in DMD, we think that these patients are at risk and that, in particular, suxamethonium and halothane should be avoided.

The observation of repeatedly normal CPK values 8–12 days after the acute event was unexpected. We explain this as temporary CPK depletion of muscle cells as a result of excessive "leakage" of enzyme during the acute stage of rhabdomyolysis.

Eugen Boltshauser
Beat Steinmann
Annemarie Meyer
Felix Jerusalem
Zurich, Switzerland

REFERENCES

Miller, E. D., Sanders, D. B., Rowlingson, J. C., Berry, F. A., Sussmann, M. D., and Epstein, R. M. (1978). Anaesthesia-induced rhabdomyolysis in a patient with Duchenne's muscular dystrophy. *Anesthesiology*, **48**, 146.

Reske-Nielsen, E. (1978). Malignant hyperthermia in Denmark: survey of a family study and investigations into muscular morphology in ten additional cases; in *Malignant Hyperthermia* (eds J. A. Aldrete and B. A. Britt), p. 287. New York: Grune & Stratton.

Richards, W. C. (1972). Anaesthesia and serum creatine phosphokinase levels in patients with Duchenne's pseudohypertrophic muscular dystrophy. *Anaesth. Intens. Care*, **1**, 150.

Seay, A. R., Ziter, F. A., and Thompson, J. A (1978). Cardiac arrest during anaesthesia in Duchenne muscular dystrophy. *J. Pediatr.*, **93**, 88.

Watters, G., Karpati, G., and Kaplan, B. (1977). Postanaesthetic augmentation of muscle damage as a presenting sign in three patients with Duchenne muscular dystrophy (DMD). *Can. J. Neurol. Sci.*, **4**, 228.

Br. J. Anaesth. (1980), **52**, 560

BOOK REVIEWS

Medical Problems and the Anaesthetist. By L. Kaufman and E. Sumner. Published by Edward Arnold Ltd. Pp. 156; illustrated; indexed. Price £9.95.

This book is one of the "Current Topics in Anaesthesia" series, the aims of which are to give a considered assessment of new material of particular interest to an anaesthetist. The title *Medical Problems and the Anaesthetist* is in a way a misnomer, because the contents are really a mixture of pharmacology, biochemistry, physiology and anaesthesia.

The authors should be commended for not making the mistake of giving the clinical features of the medical conditions mentioned, matter which is done well in established textbooks of medicine.

The sections on preoperative assessment of pulmonary function and that on hypertension are clear statements of the methods used to define a high-risk group of patients. However, there is no mention of the important work of Rooney on the behaviour of the various forms of bundle branch block during general anaesthesia. Also missing is the work of Singh and Vaughan Williams who have clarified the mechanisms of the drug treatment of arrhythmias.

In the endocrine section, one-fifth of a book of 150 pages is devoted to the interesting but rare condition of phaeochromocytoma, including 3¼ pages of references. This is unbalanced because much of the section is taken up by case reports. Examples 2, 3, 4, 5 and 8 show repetitively what can happen when arterial pressure control is not good. The restriction on the intraoperative use of labetolol imposed by its long half-life is not discussed. Sipple's syndrome is not mentioned. The literature on undiagnosed Addison's disease is not reviewed and reliance placed on a single personal communication. For diabetes mellitus, the more recent work of Leslie and Alberti and Thomas confirm the advice given on p. 98 and the whole discussion of diabetes is comprehensive and good. The particular hazards of salbutamol and corticosteroids (used in premature labour) to diabetic control are not mentioned.

There are very few mistakes in this book, but the omission of any discussion of renal and hepatic failure and anaesthesia seriously detract from its value. The second edition will no doubt give more content and greater depth.

D. M. Davies

Illustrated Handbook in Local Anaesthesia, 2nd edn. Edited by E. Eriksson. Published (1979) by Lloyd-Luke, London. Pp. 144; illustrated; indexed. Price £15.

The first edition of the *Handbook*, published in 1969, was an instant success, chiefly because of the brilliant drawings by Paul Buckhöj. The book has been unavailable in recent years (according to the foreword to the new edition) and an opportunity was taken for revision. The inappropriate chapters on therapeutic uses of parenteral lignocaine have been removed in favour of new accounts of local anaesthesia for endoscopy. New figures, particularly those relating to intercostal block and paracervical block, are a welcome improvement. The volume continues to be one of the most beautifully illustrated works in the anaesthetic literature. There are relatively few changes to the text—so few indeed that the clangers seem obvious. In 1969 the Karolinska Hospital had the impressive record of 50 000 spinal anaesthetics without serious neurological complication; the total appears to have remained unchanged for 10 years. In 1969 also there was the enigmatic reference "Löfström B. To be published". It is still there. Perhaps in the next edition they will tell us what is to be published, and when.

A. A. Spence

The Control of Chronic Pain. By S. Lipton. Published by Edward Arnold Ltd. Pp. 134; illustrated; indexed. Price £7.95.

This book fulfils admirably the stated aims of the General Editors of the Current Topics in Anaesthesia series. It is short, informative, easily read and relatively inexpensive. It has done the job of condensing the rapidly expanding volume of literature on this subject extraordinarily well and has provided a book of reference for the established anaesthetist who is thinking of extending his practice to the treatment of chronic pain, and a book of interest to those whose specialized interests lie elsewhere.

The author does not overenthuse about the treatment of chronic pain and correctly stresses the importance of diagnosis based on good clinical history, proper examination and relevant laboratory data, before even simple procedures and especially potentially harmful ones are embarked upon.

In the early part of the book Dr Lipton has successfully abstracted from the complexities of neurophysiological research the theories on which clinicians can base their practical approach. The gate control theory, the endogenous pain-relieving substances, the presence of opiate receptors in the central nervous system and the arrangement of the spinal laminae are reviewed alongside traditional ways of thinking about pain transmission; it is to the credit of the book that after reading these chapters there is little risk of confusion in the mind of the reader. The chapter on the organization of a pain clinic—a necessary inclusion not only for those who are interested in taking part but also for those who might want to understand why their colleagues do so—might with advantage have included a profile of the patients, their psychological make-up, the demands that they put on the clinic staff, and the difficulties in dealing with them and their families. Some advice on the medico-legal aspect of this type of work would be welcome.

The chapters on specialized techniques in the relief of chronic pain, including acupuncture and hypnotism, are necessarily brief, but they are well presented, with mention of some "tricks of the trade" adding practical reality. A lack of diagrams, for example in the section on intrathecal phenol block, is an obvious disadvantage. This is particularly noticeable in the sections describing peripheral nerve and plexus blocks—possibly all that is required is to point out the dangers of using destructive chemicals for block of peripheral nerves (with a list of those that, in the author's experience, might be attempted with these agents).

Overall, however, this is a useful book.

K. M. Rogers

Printed in Great Britain by John Wright and Sons Ltd, at The Stonebridge Press, Bristol BS4 5NU

© Macmillan Journals Ltd 1980

For premedication

In intravenous anaesthesia

For post-operative pain

pentazocine regd.

versatile non-narcotic strong analgesic

injection · tablets · capsules · suppositories

(Misuse of Drugs Act) regulations

Full information on the uses of Fortral in anaesthesia, alone or in combination with sedatives and tranquillisers, available from the Medical Information Department, Winthrop Laboratories, Surbiton-upon-Thames, Surrey. Clinical reports available on request. Fortral is a registered trade mark.

WINTHROP

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 5 *Published monthly* MAY 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27.50, Airmail £50 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

CONTENTS

PAGE

EDITORIAL: Not all the way on the Vancouver Style 469
A. A. Spence

EXPERIMENTAL

Enflurane has no effect on haemopoiesis in mice . 471
J. M. Baden, B. Egbert and S. A. Rice

Cardiorespiratory effects of high frequency intermittent positive pressure ventilation in the dog 475
M. K. Chakrabarti and M. K. Sykes

CLINICAL INVESTIGATION

Death associated with anaesthesia in Finland .. 483
M. Hovi-Viander

Clinical studies of gas exchange during ventilatory support—a method using the Siemens–Elema CO_2 Analyzer 491
S. G. Olsson, R. Fletcher, B. Jonson, L. Nordstrom and O. Prakash

Comparative effects of calcium chloride and calcium gluceptate 501
L. J. Drop and D. J. Cullen

Chronic hypercalcaemia, secondary to hyperparathyroidism: a risk factor during anaesthesia? 507
M. A. Gutist and L. J. Drop

Investigation of glycopyrrolate as a premedicant drug 513
A. Sengupta, P. K. Gupta and K. Pandey

I.v. flunitrazepam and i.v. diazepam in conservative dentistry. *A cross-over trial* 517
R. A. Dixon, N. R. Bennett, M. J. Harrison, C. Kenyon and J. A. Thornton

Comparison of the cardiovascular effects of bolus *v.* incremental administration of thiopentone . 527
J. L. Seltzer, J. I. Gerson and F. B. Allen

PAGE

Pancuronium in Caesarean section and its placental transfer 531
E. Abouleish, L. B. Wingard, S. de la Vega and N. Uy

Plasma concentration and metabolism of phenoperidine in man 537
L. Milne, N. E. Williams, T. N. Calvey, G. R. Murray and K. Chan

Prolonged infusion of chlormethiazole in intensive care 541
D. B. Scott, D. Beamish, I. N. Hudson and K.-G. Jostell

APPARATUS

A new nerve stimulator (Myotest) 547
J. Viby-Mogensen, P. H. Hansen, B. C. Jørgensen, H. Ørding, T. Kann and B. Fries

Evaluation of the Datex CD-101 and Godart Capnograph Mark II infra-red carbon dioxide analysers 551
J. P. Blackburn and T. R. Williams

Temperature alarm and cut-out system for use with heated water humidifier 557
P. Whitehurst and D. St Andrew

CORRESPONDENCE

Regurgitation during laparoscopy 559
Anaesthesia-induced rhabdomyolysis in Duchenne muscular dystrophy 559

BOOK REVIEWS

Medical Problems and the Anaesthetist 560
Illustrated Handbook in Local Anaesthesia .. 560
The Control of Chronic Pain 560

EDITORIAL BOARD page ii

© MACMILLAN JOURNALS LTD, 4 LITTLE ESSEX STREET, LONDON WC2R 3LF

British Journal of Anaesthesia

Editor of General Issues: A. A. Spence

For premedication

In intravenous anaesthesia

For post-operative pain

pentazocine regd.

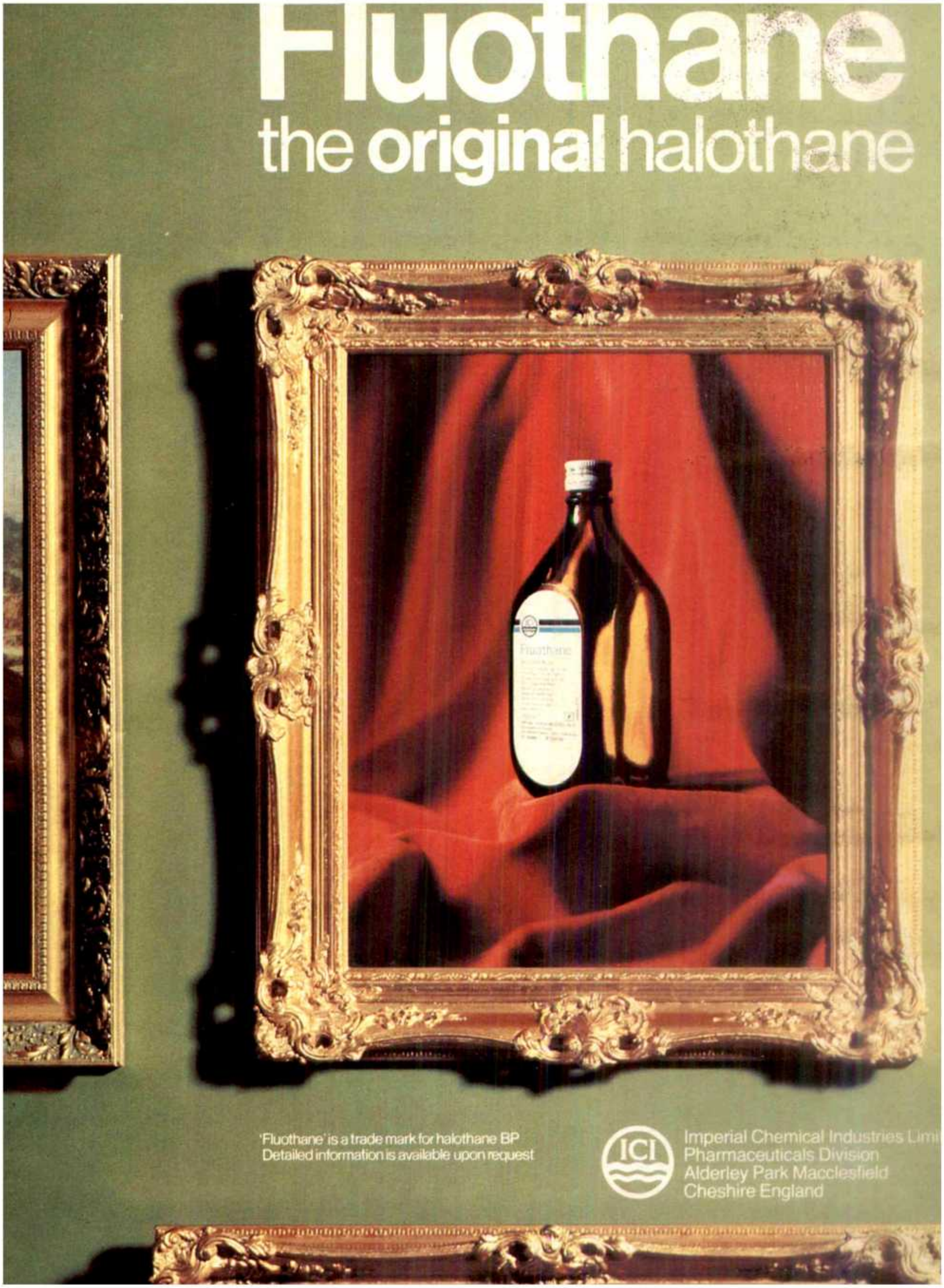
versatile non-narcotic strong analgesic

injection · tablets · capsules · suppositories

(Misuse of Drugs Act) regulations

Full information on the uses of Fortral in anaesthesia, alone or in combination with sedatives and tranquillisers, available from the Medical Information Department, Winthrop Laboratories, Surbiton-upon-Thames, Surrey. Clinical reports available on request. Fortral is a registered trade mark.

WINTHROP



'Fluothane' is a trade mark for halothane BP
Detailed information is available upon request

ICI
Imperial Chemical Industries Limi
Pharmaceuticals Division
Alderley Park Macclesfield
Cheshire England

EDITORIAL BOARD

Editor of General Issues

A. A. SPENCE, *Reader, University Department of Anaesthesia, Western Infirmary, Glasgow*

Editor of Postgraduate Educational Issues

J. NORMAN, *Professor of Anaesthetics, The General Hospital, Tremona Road, Southampton SO9 4XY*
C. M. CONWAY, *Professor of Anaesthesia, Westminster Hospital, London*
E. A. COOPER, *Professor of Anaesthesia, University of Newcastle upon Tyne; Honorary Consultant Anaesthetist, Newcastle University Hospitals*
J. W. DUNDEE, *Professor of Anaesthesia, Queen's University of Belfast*
F. R. ELLIS, *Reader in Anaesthesia, University of Leeds*
W. FITCH (Assistant Editor), *Senior Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*
G. M. HALL, *Senior Lecturer in Anaesthetics, University of London, Royal Postgraduate Medical School*
C. J. HULL, *Senior Lecturer in Anaesthesia, University of Newcastle*
A. R. HUNTER (Chairman), *Professor of Anaesthesia, University of Manchester*
D. G. MCDOWALL, *Professor of Anaesthesia, University of Leeds*
W. W. MAPLESON, *Professor of the Physics of Anaesthesia, Welsh National School of Medicine, University of Wales*
J. F. NUNN, *Head of Division of Anaesthesia, Clinical Research Centre, Harrow; Honorary Consultant Anaesthetist, Northwick Park Hospital*
J. P. PAYNE, *British Oxygen Research Professor of Anaesthetics, Royal College of Surgeons of England*
C. PRYS-ROBERTS, *Professor of Anaesthetics, University of Bristol*
J. E. RIDING (Hon. Treasurer), *Consultant Anaesthetist, United Liverpool Hospitals; Honorary Lecturer in the Department of Anaesthesia, University of Liverpool*
J. G. ROBSON, C.B.E. *Professor of Anaesthetics, University of London, Royal Postgraduate Medical School*
D. B. SCOTT, *Consultant Anaesthetist, Royal Infirmary Edinburgh*
G. SMITH, *Professor of Anaesthesia, The General Hospital, Leicester*
M. K. SYKES, *Professor of Clinical Anaesthesia, Royal Postgraduate Medical School, London*

Editorial Assistants

KIRSTEEN M. S. DEWAR, *Consultant Anaesthetist, Western Infirmary, Glasgow*
G. N. C. KENNY, *Lecturer, University Department of Anaesthesia, Royal Infirmary, Glasgow*

Papers for publication and all editorial communications should be addressed to the Editor, University of Glasgow, Department of Anaesthesia, Western Infirmary, Glasgow G11 6NT; business communications to the publishers: Macmillan Journals Ltd, 4 Little Essex Street, London WC2R 3LF.
The GUIDE TO CONTRIBUTORS can be found on pages x, xii & xiv of the advertisement section of this issue.
Published monthly. Annual subscriptions: U.K. £22·50, U.S.A. and Canada U.S.$54, Airmail U.S.$120; Rest of World £27·50, Airmail £50; (or equivalent in any other currency). ISSN 0007–0912. Orders must be accompanied by remittance. Prices correct at time of publication. Cheques should be made payable to Macmillan Journals Ltd: Subscription Department, Brunel Road, Basingstoke, Hampshire RG21 2XS, England.
Overseas subscribers may make payments into U.K. Post Office Giro Account No. 519 2455. Full details must accompany the payment.
Second Class Postage Paid New York, N.Y. U.S. Mailing Agent: Expediters of the Printed Word, Ltd, PO Box 1305, Long Island City, N.Y. 11101.

All enquiries concerning advertising should be addressed to Advertisement Department, Macmillan Journals Ltd, 4 Little Essex Street, London WC2R 3LF. (Telephone 01-836 6633). © Copyright: Macmillan Journals Ltd, 1980.

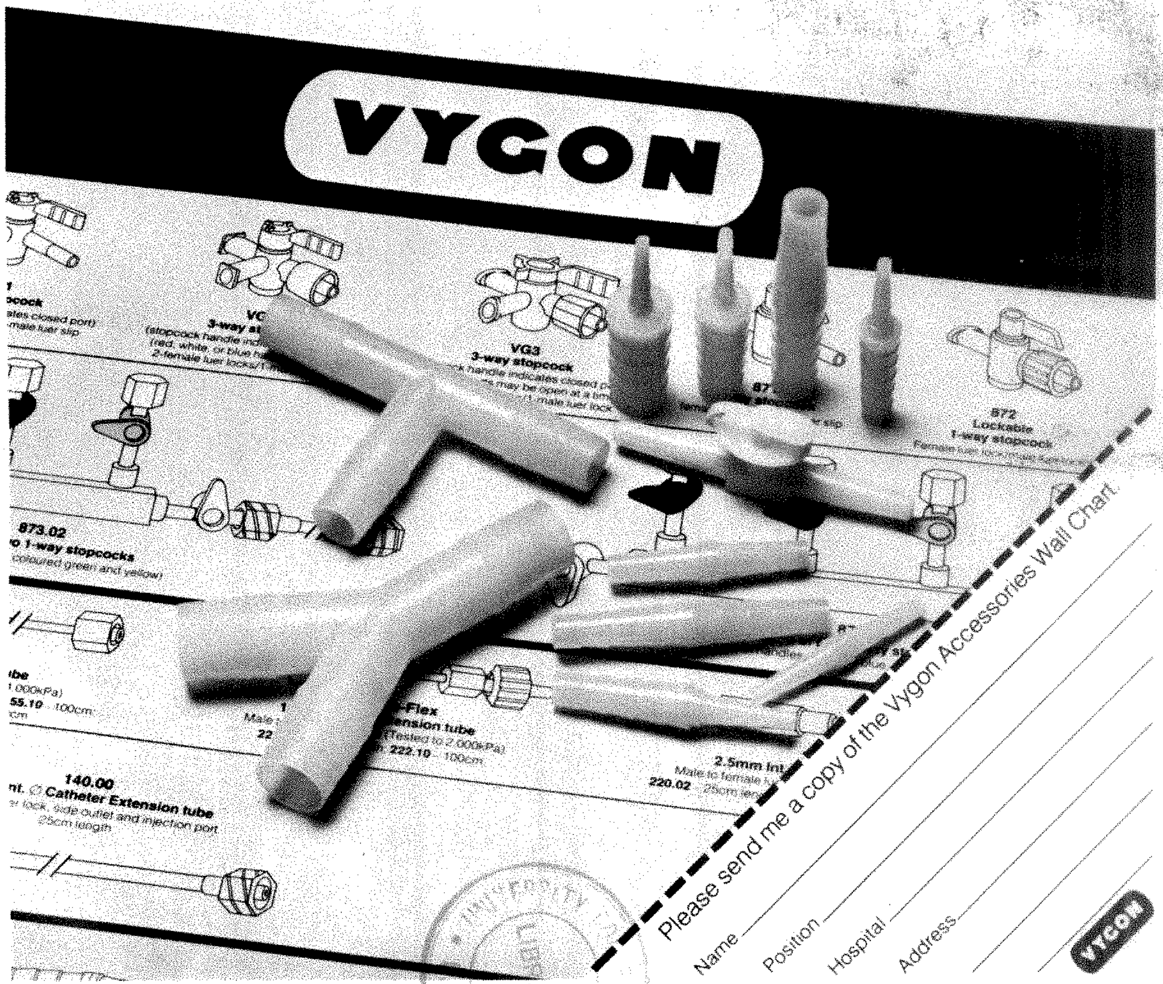
Registered Office: 4 Little Essex Street, London WC2R 3LF

Are you well connected?

Then you must be using Vygon straight, 'T' or 'Y' connectors; part of a comprehensive range of accessories, including extension tubes and stopcocks, for use in intravenous therapy and many other procedures. Quality, precision made, disposable items supplied sterile, individually wrapped (or non-sterile in bulk) to meet the most demanding requirements.

Vygon now offers for your convenience a fully illustrated Accessories Wall Chart showing the complete range available. This can be obtained from Vygon by completing the coupon below and sending it to:

Vygon (UK) Limited,
Bridge Road, Cirencester,
Gloucestershire GL7 1PT.
Telephone: Cirencester (0285) 67051



Please send me a copy of the Vygon Accessories Wall Chart.

Name

Position

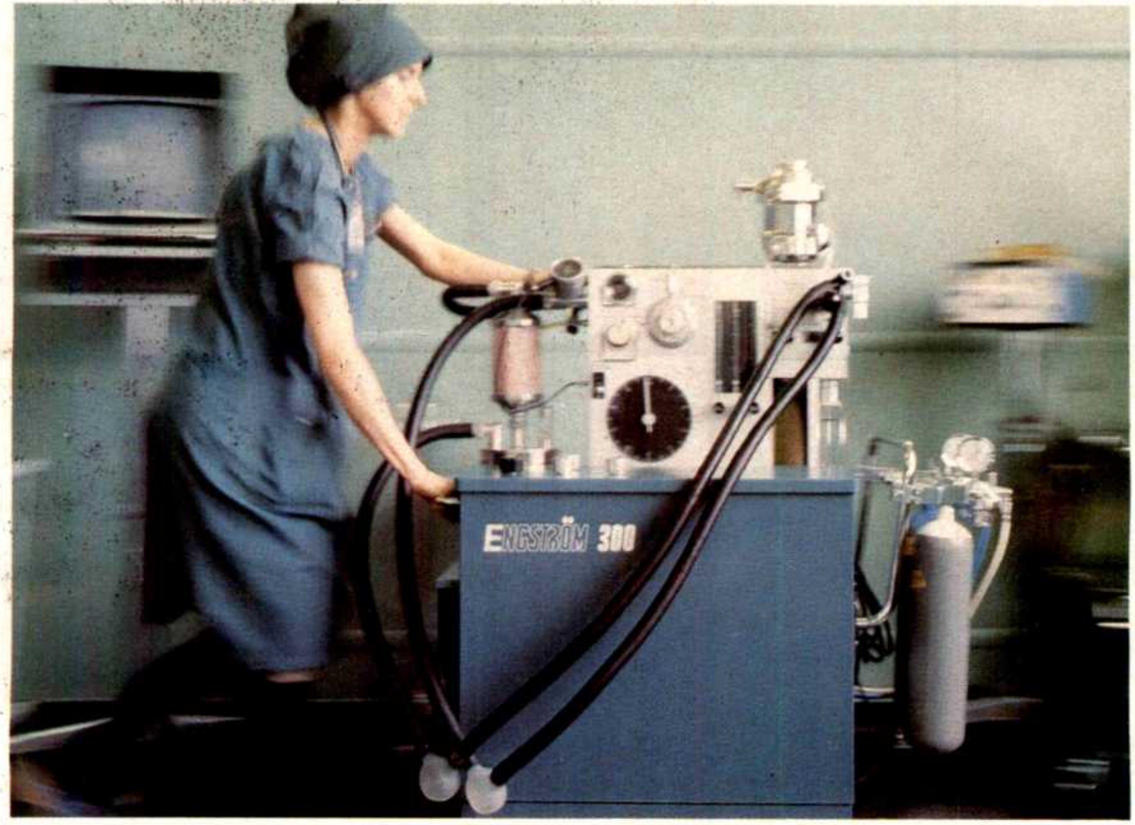
Hospital

Address

VYGON

UNIVERSITY LIBRARY

Just wheel it to where you need it.



Plug it into the mains, and it's ready to work.

The Engström 300 can operate as a completely self-contained unit. It can carry its own supplies of gas, and has its own built-in driving compressor.

It is an all-purpose respirator. Models are available for both adults and children, and accessories make it easily adaptable for intensive care or anaesthesia.

Operation is simple. All settings are easy to make. The respirator automatically adapts to changes in the lungs of the patients.

All parts are designed to withstand much more than their share of hard use. Preventative maintenance and repair is done with simple tools.

These are some of the reasons why hospitals all over the world swear by their Engströms. We would like you to see for yourself. Contact your nearest Engström representative for more information, and you'll get our new brochure. Or, if you would like to see it demonstrated on your own ground, he will arrange an appointment at your convenience.

ENGSTRÖM

Engström Medical AB,
Box 1295, S-17125 Solna, Sweden.

Engström 300 - the self-contained, all-purpose respirator for routine clinical use.

Patients are quick to sit up and take notice after

ALTHESIN

(alphaxalone and alphadolone acetate)

the anaesthetic for short procedures

Recovery is outstandingly good, rapid and progressive

"Althesin appears to be an excellent induction agent."[1]

Althesin provides a rapid and pleasant recovery with a low incidence of hangover.[1]

Patient acceptance is high and the incidence of nausea and vomiting is low.[2]

"Patients from morning lists are quite able to have a full lunch, which they could not have done with any barbiturate."[3]

1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

Glaxo

Glaxo Laboratories Limited
Greenford, Middlesex
UB6 OHE

Althesin is a Glaxo trade mark

Uses
Induction of anaesthesia
Maintenance of anaesthesia
Experience is insufficient at present to advocat
use of Althesin in infants under one year, in
patients with hepatic dysfunction, and for
maintenance of anaesthesia in obstetrics.

Dosage and administration
As usual, it is recommended that patients shou
fast before receiving Althesin.
The usual intravenous dose of Althesin for bot
children and adults is between 0·05ml and
0·075ml per kilogram bodyweight, i.e., half to
three-quarters of a millilitre per 10kg.
Younger children usually require the higher do
and may need 0·075ml/kg bodyweight. Althes
should be injected slowly, taking no less than 3
seconds, as this promotes smooth induction.
Althesin has negligible analgesic activity.

Contra-indications
Previous adverse reactions to Althesin.
Hepatic failure.

Precautions
Like other anaesthetics, Althesin should only
used in the presence of an experienced
anaesthetist, and resuscitative equipment sho
be immediately available. The risk of severe
reactions (see below) may be higher in patient
with a personal or family history of atopy. Sinc
Althesin produces relaxation of the jaw muscle
the jaw requires support to prevent obstructio
the airway. Concurrent use of other depressa
the central nervous system may retard recove
full consciousness, and recovery from anaesth
should, as always, be assessed carefully befor
allowing out-patients to go home or resume no
activities. The effects of Althesin are likely to b
prolonged in patients with impaired liver func
Animal experiments show no evidence of
teratogenicity, but Althesin should be used wi
caution in pregnancy.

Side effects
Minor side-effects may include a transient flush a
muscle twitching, the latter occurring more ofte
patients given hyoscine alone as premedication.
There is a possibility of generalised convulsions,
of cardiac arrhythmias in patients concomitantly
treated with muscle relaxants. Short periods of
coughing, hiccoughing, salivation, laryngospasm
shivering may occur, particularly in association w
light anaesthesia or rapid injection.

Mild euphoria or depression sometimes occur
during recovery from Althesin anaesthesia. P
operative nausea and vomiting are infrequen
There have been occasional reports of more
severe reactions. Bronchospasm and/or a ma
drop in blood pressure may be preceded by a
generalised flushing of deep red or purplish
colour, and followed by some oedema of lips a
eyelids. Such reactions may require treatmen
with pure oxygen, intravenous corticosteroids
plasma expanders.

Overdosage
If serious respiratory depression occurs,
respiration should be supported mechanicall
margin of safety is wide, and 0·2ml/kg, or fou
times the minimum sleep dose, has been give
single dose without serious effects.

Packs
Ceramically-printed 5 or 10ml ampoules in bo
of 10 ampoules.

Product Licence number 4/0189
Price to Hospital (exclusive of VAT)
5ml 80p

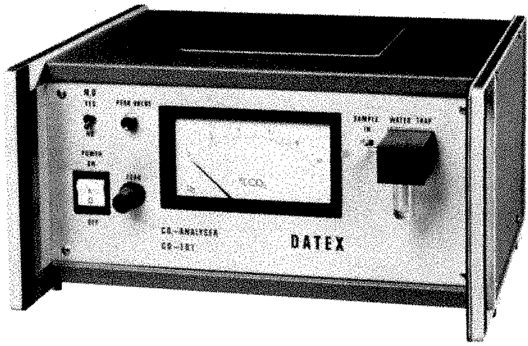
Get critical respiratory information on the spot!

The DATEX CD-101 CO_2 Analyzer continuously monitors the $\%CO_2$ in expired air, which correlates well with the partial CO_2 pressure in arterial blood. Critical information is available fast, without the need for arterial puncture.

WITH THE CD-101 YOU CAN EASILY CONTROL:

- **adequacy of ventilation (even in pediatrics)**
- **changes in circulation, respiration or metabolism**
- **effects of respiratory depressing drugs**
- **pulmonary circulation during cardiac bypass**
- **need for increased sedation**
- **weaning after anaesthesia**

Together with the CD-101, the CA-100 Capnogram Recorder allows the recording of $\%CO_2$. From this Capnogram, detailed information regarding respiration may be obtained.



DATEX

For more information contact:

Vickers Limited Medical Engineering
Priestley Road Basingstoke Hampshire England RG24 9NP
Telephone 0256 29141 Telex 858697

Institute of Basic Medical Sciences

Royal College of Surgeons of England

British Postgraduate Medical Federation (University of London)

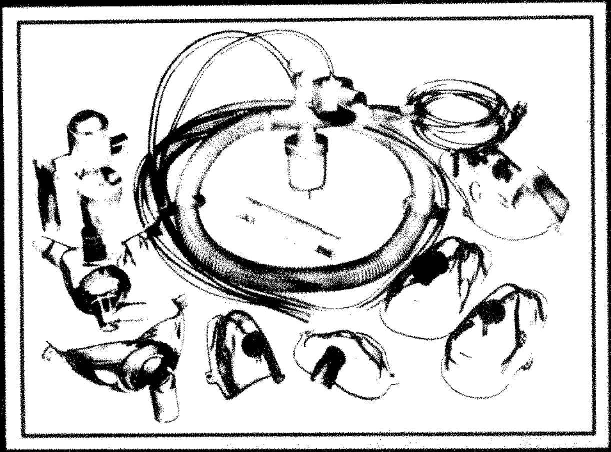
A course of study in the Basic Medical Sciences for Anaesthetists will be held at the Institute of Basic Medical Sciences from 29th December 1980 to 20th February 1981.
The course consists of a full-time programme of lectures, demonstrations and tutorial classes covering physiology, pharmacology, biochemistry and clinical measurement. It is suitable for candidates preparing for the Primary F.F.A. Examination.
The fee is £550 (subject to revision).

All the College Museums (Anatomy, Pathology, Odontological and Hunterian), in addition to the College Library, are open to course students.
All enquiries and applications should be made to:

Mr. I. Budden, Secretary,
Institute of Basic Medical Sciences,
Royal College of Surgeons of England,
Lincoln's Inn Fields,
LONDON WC2A 3PN.
Telephone: 01-405 3474 Ext. 43.

The Sandoz Lifeline range
Available in the new dispenser box

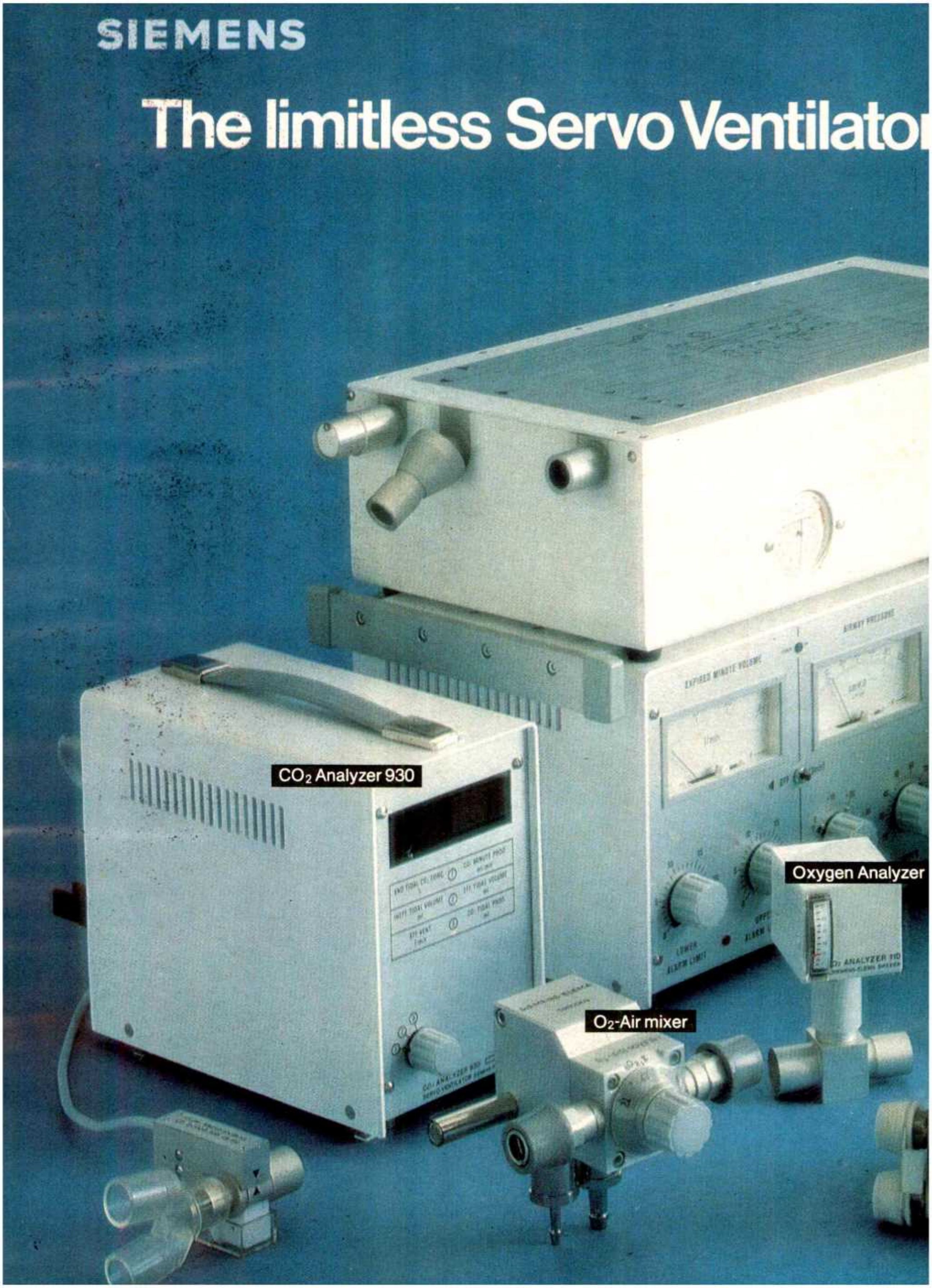
Sandoz is Lifeline, Lifeline is Sandoz



- Manufactured and assembled in the UK with a high level of quality control.
- A full range of disposables for all Oxygen/ Aerosol therapy and Ventilation.
- A handy dispenser pack which can be hung on the wall in any Unit.
- Fast and reliable delivery service.
- Quality products at competitive prices.

Another first from Sandoz.

medical equipment division


SIEMENS
The limitless Servo Ventilato
CO_2 Analyzer 930
Oxygen Analyzer
O_2-Air mixer

ystem.

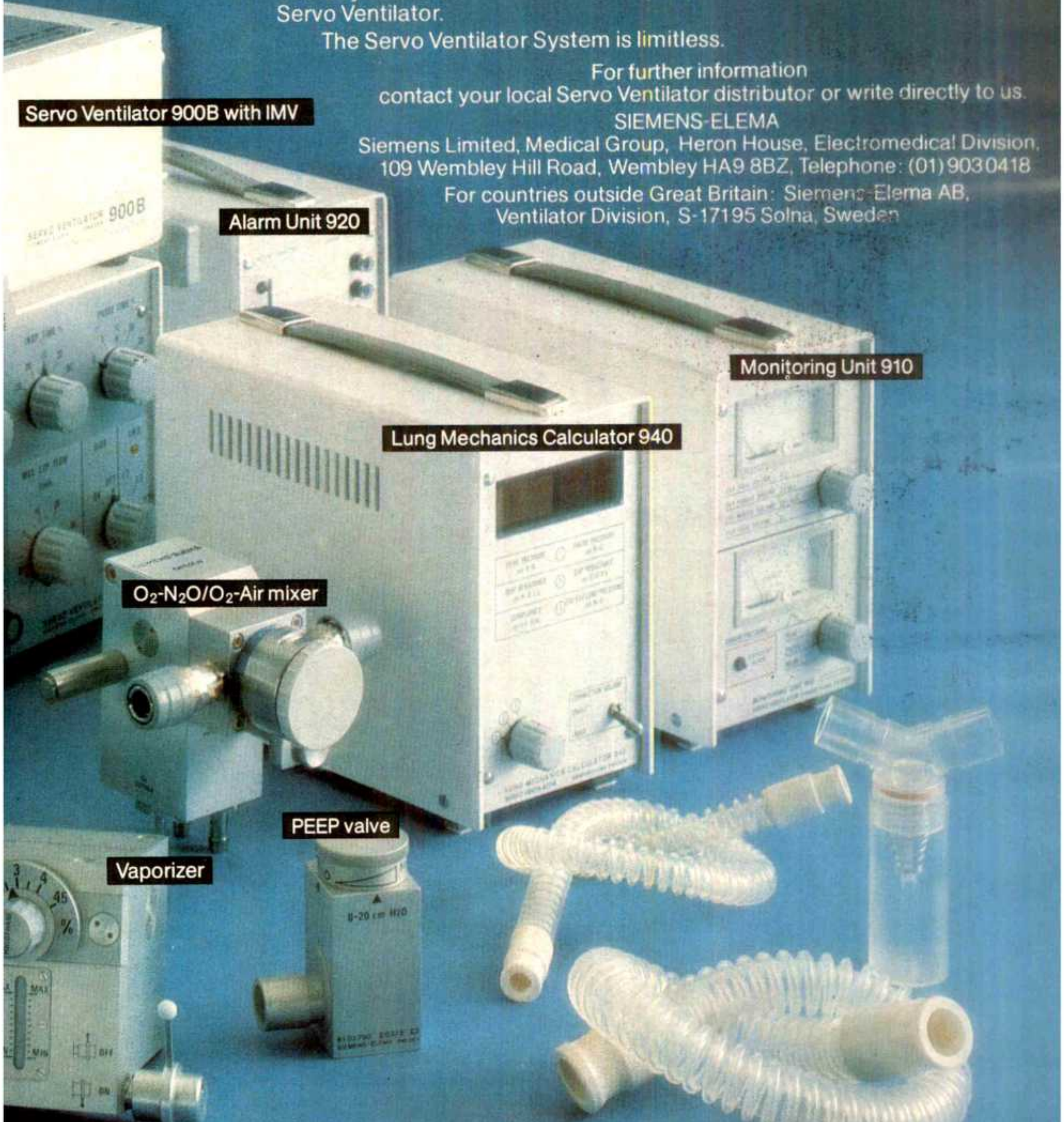
A complete system that has no limits for respiratory care and corresponds to the experienced clinician's entire capabilities.

The Servo Ventilator System provides instantaneous diagnostic possibilities through the CO_2 Analyzer and Lung Mechanics Calculator. The clinician can concentrate all his resources on immediate actions to save his patient, without restrictions or improvisations.

Thanks to the electronics, new devices developed from research of today and tomorrow are easy to build in or connect to the Servo Ventilator.

The Servo Ventilator System is limitless.

For further information
contact your local Servo Ventilator distributor or write directly to us.
SIEMENS-ELEMA
Siemens Limited, Medical Group, Heron House, Electromedical Division,
109 Wembley Hill Road, Wembley HA9 8BZ, Telephone: (01) 903 0418
For countries outside Great Britain: Siemens-Elema AB,
Ventilator Division, S-171 95 Solna, Sweden



Servo Ventilator 900B with IMV
Alarm Unit 920
Monitoring Unit 910
Lung Mechanics Calculator 940
O₂-N₂O/O₂-Air mixer
PEEP valve
Vaporizer
Steam autoclavable tubings, water traps and Y-pieces
SERVO VENTILATOR 900B

GUIDE TO CONTRIBUTORS

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. Two issues each year deal mainly with material of postgraduate educational value.

PAPERS

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publishers.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted.

LEGAL CONSIDERATIONS

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

PREPARATION OF MANUSCRIPT

Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full addresses) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

Title page

There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spaces should also be suggested.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the experiments to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of experimental results, while concise, should permit repetition of the experiments by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of

ORGANON TEKNIKA
INFORMATION SERVICE

Neuromuscular
Transmission &
Anaesthetic Agents

This quarterly pocket edition is intended as a convenient aid to the anaesthetist interested in current progress with neuromuscular transmission and drugs.

Each edition carries a special feature, a bibliography of current publications concerning anaesthetic agents and a suggested list of further reading. The information is elicited from 27 current journals.

If you would like to receive a copy regularly or copies of previous editions please contact:

ORGANON TEKNIKA

Organon Teknika Limited, Teknika House,
Cromwell Road, St. Neots,
Cambridgeshire. PE19 2HS

Tel. No. Huntingdon (0480) 76963

A service from the manufacturers
and distributors of Pavulon pancuronium bromide
–the muscle relaxant of choice

digits should be avoided. Significance should be given as values of probability. The desired positions of tables and figures may be indicated by written instructions enclosed within lines and brackets, for example:

(TABLE III near here)

Discussion

The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially.

References

There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

In the case of books, the reference should be as follows: name of author and initials; year of publication in parentheses; title of book, underlined; number of edition; page number; town of origin, publisher; for example: Hill, D. W. (1971). *Physics Applied to Anaesthesia*, 2nd edn, p. 212. London: Butterworths.

The *British Journal of Anaesthesia* should be referred to as *Br. J. Anaesth.*

In the text up to three authors should be named before the use of ". . . et al.". If reference is made to several publications during a particular year, written by a larger group of authors who have alternated the order of authorship, as many names must be written as are necessary to distinguish between the publications, before use of ". . . et al." in conjunction with the year suffixes a, b, c.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase "(in press)" replacing volume and page number.

It is essential that authors verify the content and details of references which they list, as this responsibility cannot be accepted by either Editors or Publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with roman numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used.

Illustrations

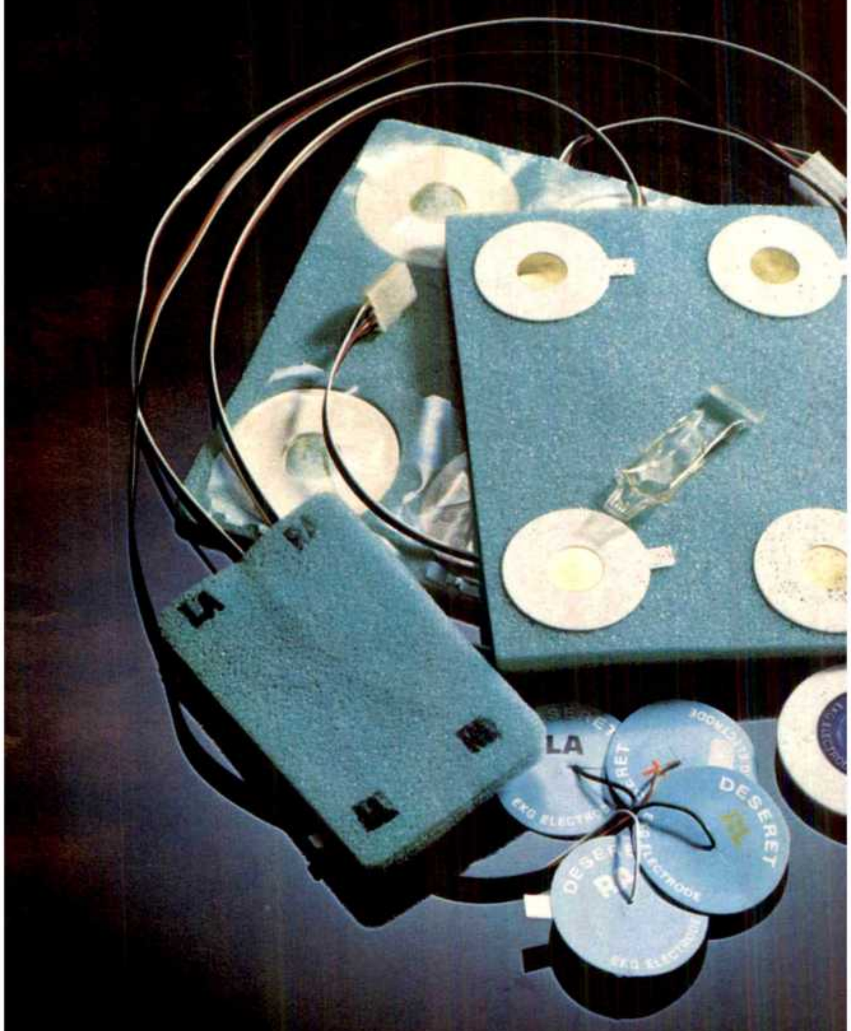
Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black india ink on white paper. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using arabic numerals. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ ◐
◑ ◒ ◉ ⊙ ⦶ ⊕ ⊖ ▩ ■ ▤ × +

The name of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It is emphasized that care taken in the original preparation of figures will obviate the time-consuming and expensive necessity of their revision.

DESERET



EKG Pads and Electrodes

high-quality range, with a wide variety of cables and

- Reliable adhesion and contact.
- Maximum patient comfort.
- Available in adult and paediatric sizes.

ase telephone or write to us for full details:

General information

Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available:

1.	PART I	(capitals)
2.	RESULTS	(small capitals)
3.	Blood-gas analysis	(l.c. roman)
4.	*The action of drugs*	(italics, centre)
5.	*Lung function studies*	(italics, full out)
6.	*Volume*. Large volumes. . . .	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet "Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors" (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

CORRESPONDENCE

It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

PROOFS

These should be corrected and returned to the sub-editor *within 48 hours of receipt*. Overseas contributors should return their proofs by airmail.

REPRINTS

Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

Pain: a novel approach...

The revolutionary Lloyd-Neurostat. A major breakthrough in the treatment of intractable, acute and chronic pain from Spembly.

Spembly have used their unequalled experience in cryosurgery to develop a system which locates and freezes peripheral nerves, giving a long-term reversible block with low incidence of neuroma and neuritis.

The technique is called cryoanalgesia, and clinical research is constantly exploring new applications.

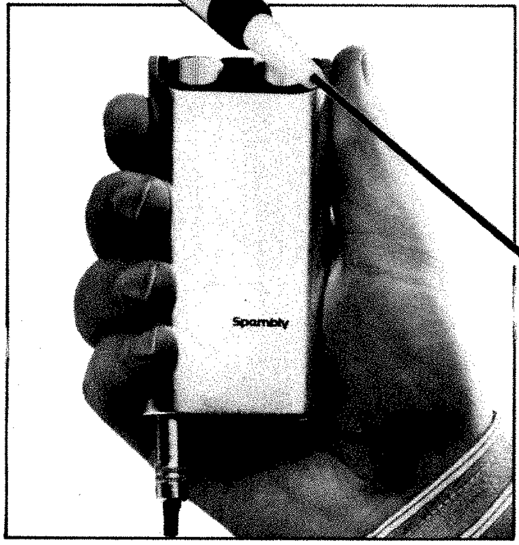
Another form of non-drug treatment is the Spembly 9000, a highly effective TENS system.

TENS provides a low-risk, non-invasive technique for symptomatic relief of pain of many different etiologies.

A combination of advanced specification and high performance at economic cost make the 9000 range one of the finest available.

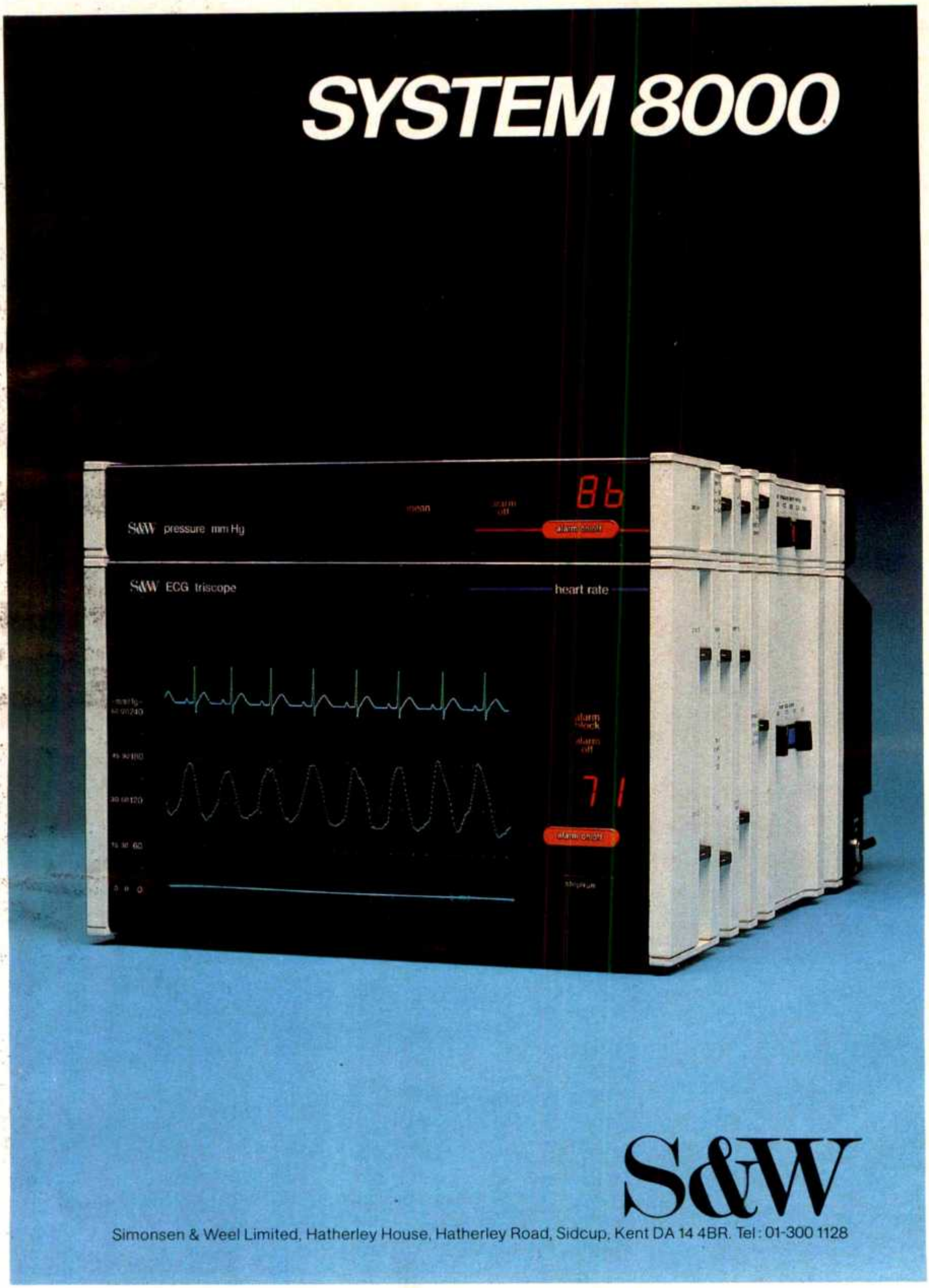
For further information on Spembly products phone Andover 65741.

And get the facts from Mike Alderson.



Spembly

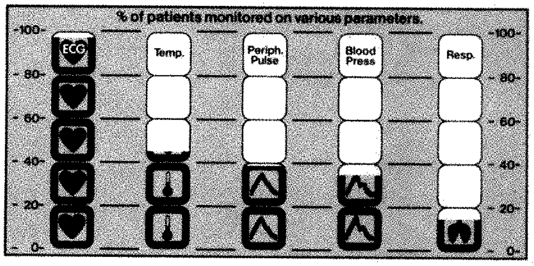
Spembly Limited
Newbury Road Andover Hampshire SP10 4DR England
telephone (0264) 65741 telex 47403



Simonsen & Weel Limited, Hatherley House, Hatherley Road, Sidcup, Kent DA 14 4BR. Tel: 01-300 1128

...a different approach to Patient Monitoring

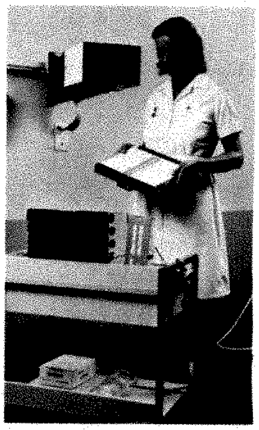
Electronic monitoring is now an accepted part of patient care. ECG is the most regularly monitored signal and the table below approximates to the percentage of patients monitored electronically for the more common parameters.



Today the cost of quality medical instrumentation does not allow there to be equipment in the Intensive or Coronary Care Unit which is not fully used or is unavailable for use on one patient because it is locked into a system on another. The S & W 8000 System allows total flexibility to match the instrumentation to the patient's need with the added advantages of:-

- * Progressive expansion of the monitoring system as new modules for new parameters are developed
- * Modules may be used with a low cost power supply as monitors in their own right; for example, pressure, temperature, respiration
- * May be used in any department in the hospital; C.C.U., I.T.U., Operating Theatres, Neo-natal units
- * Ease of servicing in event of unsatisfactory performances

The 8000 System is built to the high standards of safety and incorporates the recent advances in technology. Quality and reliability have been major design considerations. Let us show you how patient monitoring equipment should be made.



The 8000 System has been awarded the Industrial Design Award for 1979 and the Danish Plastics Industry Design prize 1979

analgesia by peridural & spinal opiates

International congress 20 - 21 November 1980 University of Nijmegen, The Netherlands.

Presentation of basic research on the endorphin system with the topics neuroanatomy, neurophysiology, neuropharmacology and neuropeptides. Evaluation of the clinical results of peridural and spinal opiate application in anaesthesiology against the background of basic research.

Organization:

Department of anaesthesiology,
G. M. M. Nijhuis

Department of pharmacology,
A. L. Cools.

Speakers:

B. Bohus, Ph.Bromage (honorary adviser), C. Devaus, R. Dirksen, A. J. Kastin, R. A. North, G. M. M. Nijhuis, J. M. van Rossum, J. C. Schwartz, P. E. Voorhoeve, T. L. Yaksh.

For registration and information:

Ine Baltussen,
Dept. of Anaesthesiology,
University of Nijmegen,
Postbox 9101,
6500 HB Nijmegen (The Netherlands).
Tel. No.: 080-514553.

THE SECOND ASIAN CONGRESS OF ANAESTHESIOLOGISTS

September 11–13, 1981 Kuala Lumpur, Malaysia

Further information:

Dr S. W. Lim,
Malaysian Society of Anaesthesiologists,
MMA Secretariat,
P.O. Box S-20 Sentul,
124 Jalan Pahang,
Kuala Lumpur 02–14,
Malaysia.

ASIAN ARCHIVES OF ANAESTHESIOLOGY AND RESUSCITATION 2ND INTERNATIONAL CONFERENCE ON CRITICAL CARE MEDICINE

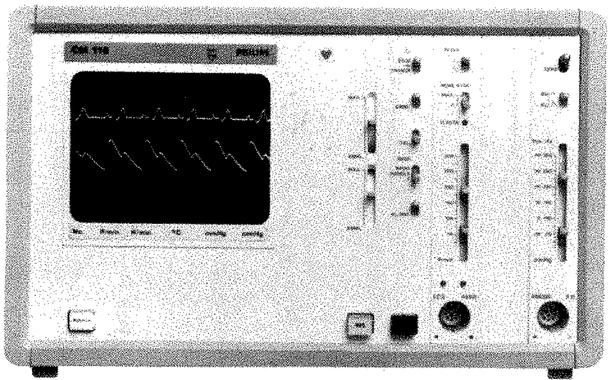
New Delhi, India November 22–27, 1980

The conference (theme: Disaster Medicine) and a course in advances in cardiopulmonary resuscitation will be held at Vigyan Bhavan, Maulana Azad Road, New Delhi.

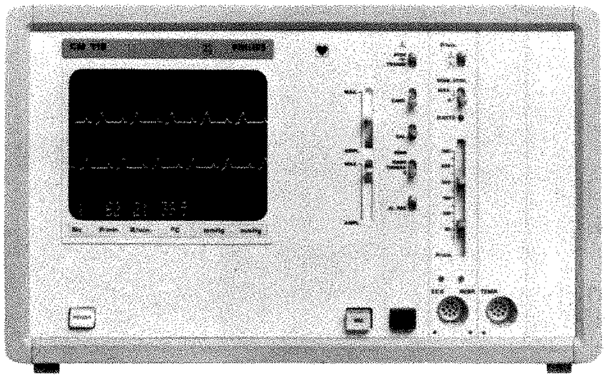
Details available from:

Prof. (Dr) N. P. Singh,
Conference Convenor,
National Association of Critical Care Medicine,
Department of Anaesthesiology and Resuscitation,
Willingdon Hospital,
New Delhi 110001, India.

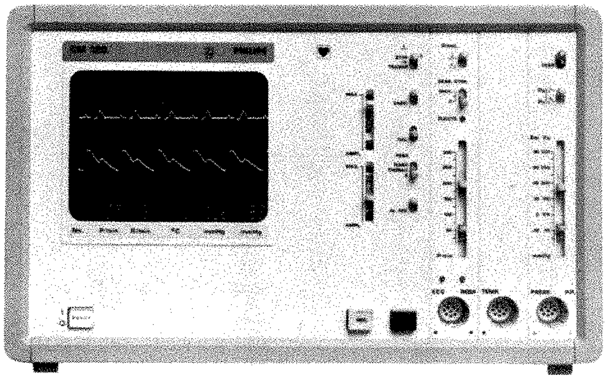
EFFICIENT PATIENT MONITORING



CM116



CM118



CM120

Philips give you a Compact choice

In fact it's from three truly compact, efficient and flexible patient monitoring systems. Each designed to provide an increasing amount of data – from the new CM 116 and CM 118 through to the comprehensive CM 120. All three monitors feature a large 10 x 14cm screen with a 5.7 second trace length, and provide essential answers at an economic price.

The CM 120 distinctively displays no less than five numeric read-outs, plus the Patient's Bed Number, and two traces. The lower trace offers a choice of four alternatives. There are also alarm features which are built-in as standard.

Philips Compact Monitors are all built to the highest safety standards, and offer high resistance to HF interference on all parameters. Printed confirmation of data can be obtained by linking to any of the Philips range of trace recorders. And all three Compact Monitors can be used in a mixed installation situation – achieving considerable savings through the selection of the right unit for each range of applications.

PHILIPS COMPACT MONITORS

... three small contributions to more efficient patient monitoring

For detailed information, write to:
Philips Medical Systems,
Kelvin House, 63/75 Glenthorne Road,
Hammersmith, London W6 0LJ.
Telephone: 01-741 1666.

PHILIPS Medical Systems

PHILIPS

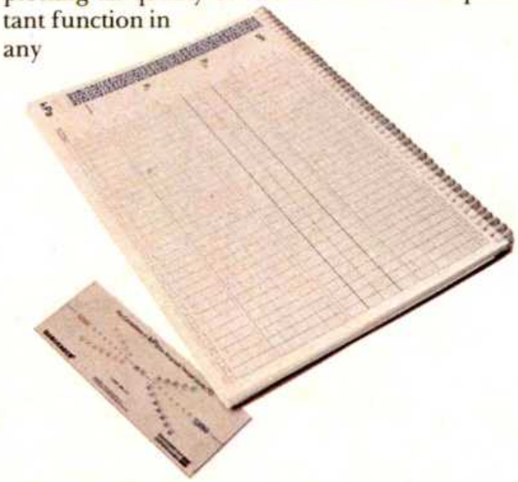
Qualicheck.®

A quality control program
developed by the worlds most experienced producer
of blood gas analyzers.

Dispenser
The Radiometer Qualicheck® System reflects our experience as a leader in the blood gas field. The unique dispenser, for example, assures anaerobic transfer of the quality control liquid to the analyzer.

Control Liquids
Qualicheck® includes three different check solutions covering the clinically significant levels. The bright color coding of all material eliminates potential confusion. Each batch of Qualicheck® is carefully analyzed so that assigned values for each level become an integral part of Radiometer's total quality assurance program. The solutions are sealed in single-use ampoules, providing the most favorable conditions for your quality control measurements.

Data Collection
The Qualicheck® logbook is convenient for plotting all quality control results – an important function in any quality control program. All pages – again properly color coded – will, when used on a regular basis, allow for a safe and quick evaluation of an analyzer's reliability. The temperature templet reduces errors due to room temperature variations and eliminates the need for a constant temperature bath.



– for more about Qualicheck®
Qualicheck®, Radiometer's quality control system, results from our experience in developing and producing blood gas instrumentation. Contact your local Radiometer representative for details on Qualicheck® and quality control.

RADIOMETER
COPENHAGEN
Radiometer A/S · 72 Emdrupvej
DK-2400 Copenhagen NV · Denmark

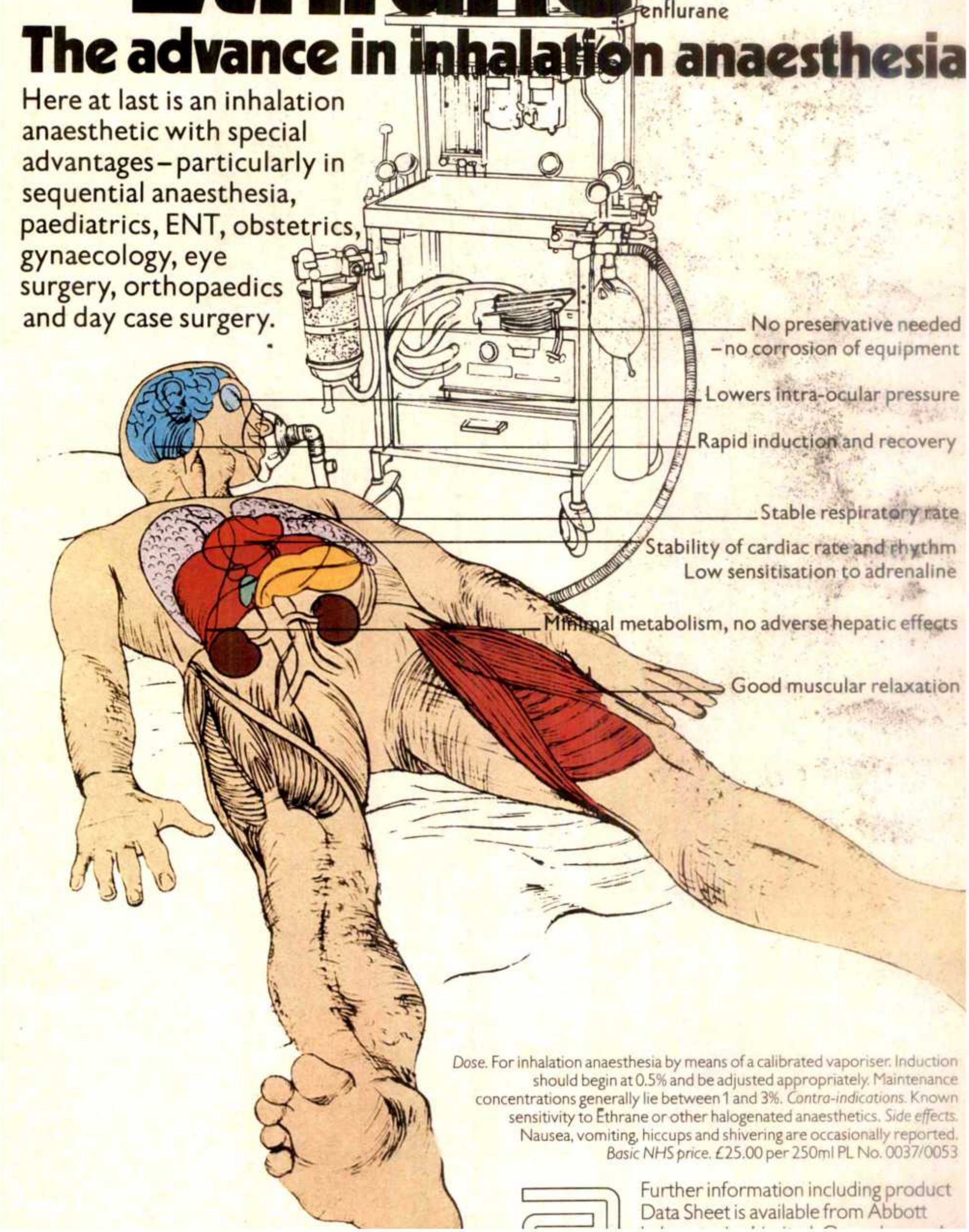
J+J industrial advertising/Copenhagen

Ethrane®

enflurane

The advance in inhalation anaesthesia

Here at last is an inhalation anaesthetic with special advantages – particularly in sequential anaesthesia, paediatrics, ENT, obstetrics, gynaecology, eye surgery, orthopaedics and day case surgery.



No preservative needed
– no corrosion of equipment
Lowers intra-ocular pressure
Rapid induction and recovery
Stable respiratory rate
Stability of cardiac rate and rhythm
Low sensitisation to adrenaline
Minimal metabolism, no adverse hepatic effects
Good muscular relaxation

Dose. For inhalation anaesthesia by means of a calibrated vaporiser. Induction should begin at 0.5% and be adjusted appropriately. Maintenance concentrations generally lie between 1 and 3%. *Contra-indications.* Known sensitivity to Ethrane or other halogenated anaesthetics. *Side effects.* Nausea, vomiting, hiccups and shivering are occasionally reported. *Basic NHS price.* £25.00 per 250ml PL No. 0037/0053

Further information including product Data Sheet is available from Abbott

Senior Medical & Health Officers (Anaesthesia)

Hong Kong £11,140 p.a. + 25% gratuity

- Maximum tax 15%
- Medical benefits
- Dental benefits
- Free passages
- Generous annual leave
- Subsidised accommodation
- Children education allowances
- Holiday visits for children

Applications are invited for appointment as Senior Medical & Health Officers (Anaesthesia) in the Medical & Health Department, Hong Kong. Successful candidates will manage anaesthesia to patients (including dental patients), undergoing operations in government hospitals including pre-operative and post-operative visits to patients in the wards and train junior anaesthetists and nurses.

Applicants must have a medical qualification registrable with the British Medical Council and a higher medical qualification in Anaesthesia plus 5 years' post-registration experience. Experience in dental anaesthesia will be an advantage and preference will be given to candidates who can speak both Cantonese and English.

The appointment will be for an initial agreement of 3 years. The salary scale is from HK$10,400 to HK$11,200 per month (approximately £11,140 to £12,000 p.a.*).

For further information and application form, write to the Hong Kong Government Office, 6 Grafton Street, London W1X 3LB, quoting reference MD/SMHO at the top of your letter. Closing date for return of application forms: 30 June 1980.

**Based on exchange rate HK$11.20 £1.00.*
This rate is subject to fluctuation.

Hong Kong Government

Der Anaesthesist

The organ of the
Austrian, German and Swiss Societies
of Anaesthesiology and Reanimation

Edited by: A. Doenicke, Mpnchen; R. Frey, Mainz; O. Mayrhofer, Wein; H. Schaer, Mennedorf
Managing Editor: A. Doenicke, Mpnchen, Chirurgische Universitets-Poliklivik, Anaesthesie, Pettenkoferstr. 8a, D-8000, Mpnchen

Contents

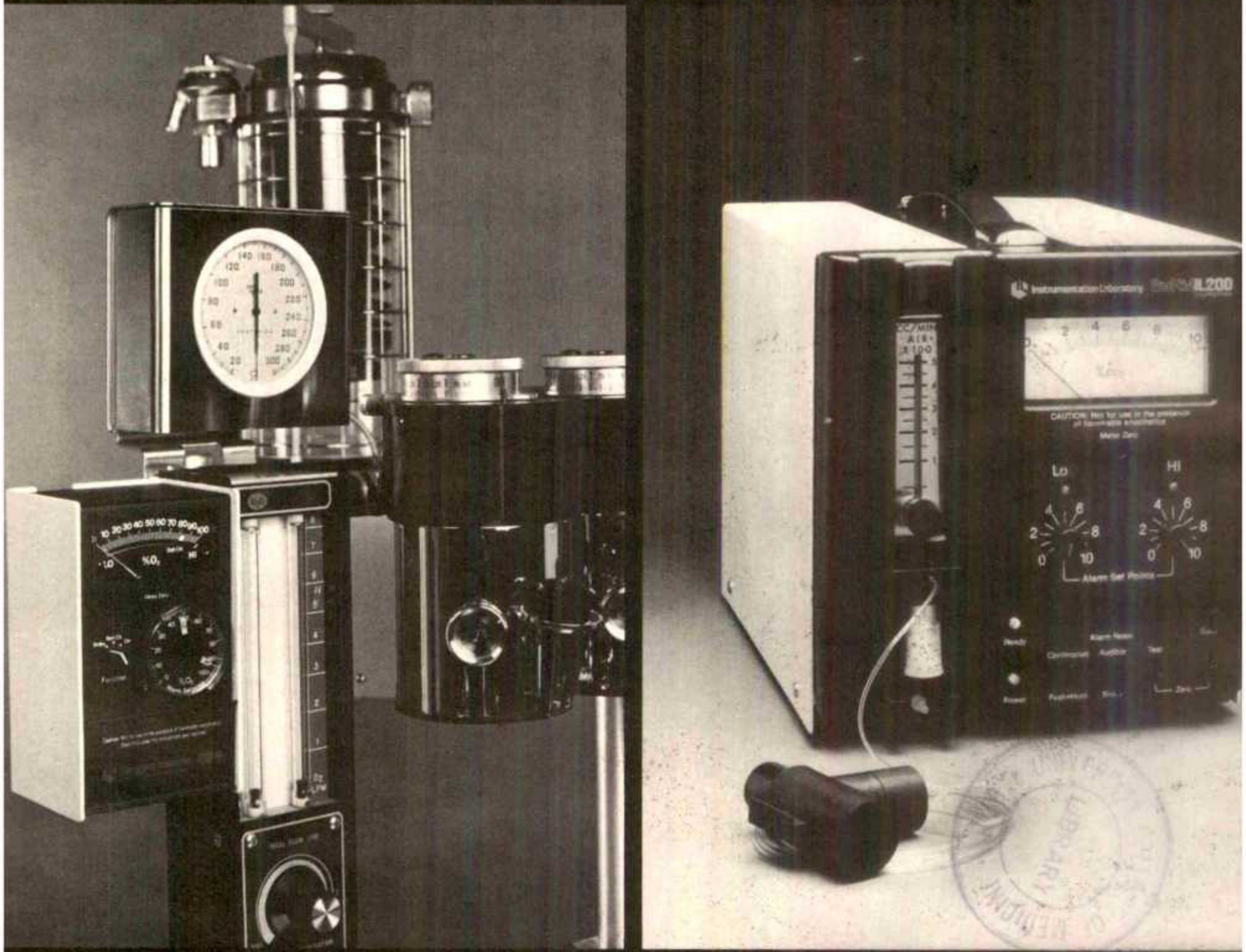
APRIL 1980

P. M. Suter	"Optimal" regulation of mechanical ventilation	163
K. J. Falke	Do changes in lung compliance allow the determination of "Optimal PEEP"?	165
H. F. Cascorbi, J. M. Vento	Toxic properties of an isomer of halothane	169
R. Hohle, H. P. Siepmann	The influence of adrenaline on the effects of halothane and enflurane on the myocardium. Papillary muscle of the cat	172
R. Dudziak, K. Bonhard	The development of haemoglobin preparations for various indications	181
U. Ottermann	Cardioplegic haemoglobin-perfusion for myocardial protection. Experiments on isolated rat-hearts	190
J. O. Arndt, F. Mameghani	The effects of etomidate, fentanyl and dehydrobenzperidol on baroreflex function. A study on dog's carotid sinusreflex	200
E. Freye, J. O. Arndt	Perfusion of fentanyl through the fourth cerebral ventricle and its cardiovascular effects in awake and halothane anesthetised dogs	208

Annual subscription: DM 180 + postage

Published by SPRINGER-VERLAG · Berlin · Heidelberg · New York

Monitor the ins *and* the outs of ventilation.



LIBRARY
MEDICINE

The new **End-tidIL™ 200 CO_2 Monitor** gives you breath-by-breath analysis of expired CO_2 at an affordable price.

For over a decade, IL has been providing anesthesiologists with products to monitor oxygen delivery. Now, the End-tidIL™ 200 CO_2 Monitor provides a safeguard for proper ventilation.

This new instrument monitors the patient's expired % CO_2 on a continuous or peak value basis to indicate:

- cardiac and pulmonary information
- hypercapnia and hypocapnia
- malfunction of the CO_2 absorber
- air embolism
- disconnected or obstructed airway
- changes in arterial P_{CO_2}

IL, the leading manufacturer of O_2 Monitors, offers this quality CO_2 Monitor at a price that makes it affordable for every patient under anesthesia to be assured of proper ventilation. For a demonstration or further information contact IL.

Instrumentation Laboratory (U.K.) Ltd.
Kelvin Close
Birchwood Science Park
Warrington, Cheshire
England
Telephone: 0925-810141
Telex: (851) 627713.

Instrumentation

Marcain
extends the frontiers of local analgesia

10 AMPOULES OF 10 ml
MARCAIN PLAIN 0.5%
INJECTION
10 AMPOULES OF 10 ml
DF
MARCAIN
PLAIN 0.5%
INJECTION
A long acting local anaesthetic
Each 10 ml ampoule contains
Bupivacaine hydrochloride BP 0.5% w/v

Marcain has been shown to produce a high incidence of successful blocks, rapid onset of action, and remarkably low systemic toxicity when used for intravenous regional analgesia. Please write for a copy of our information leaflet.

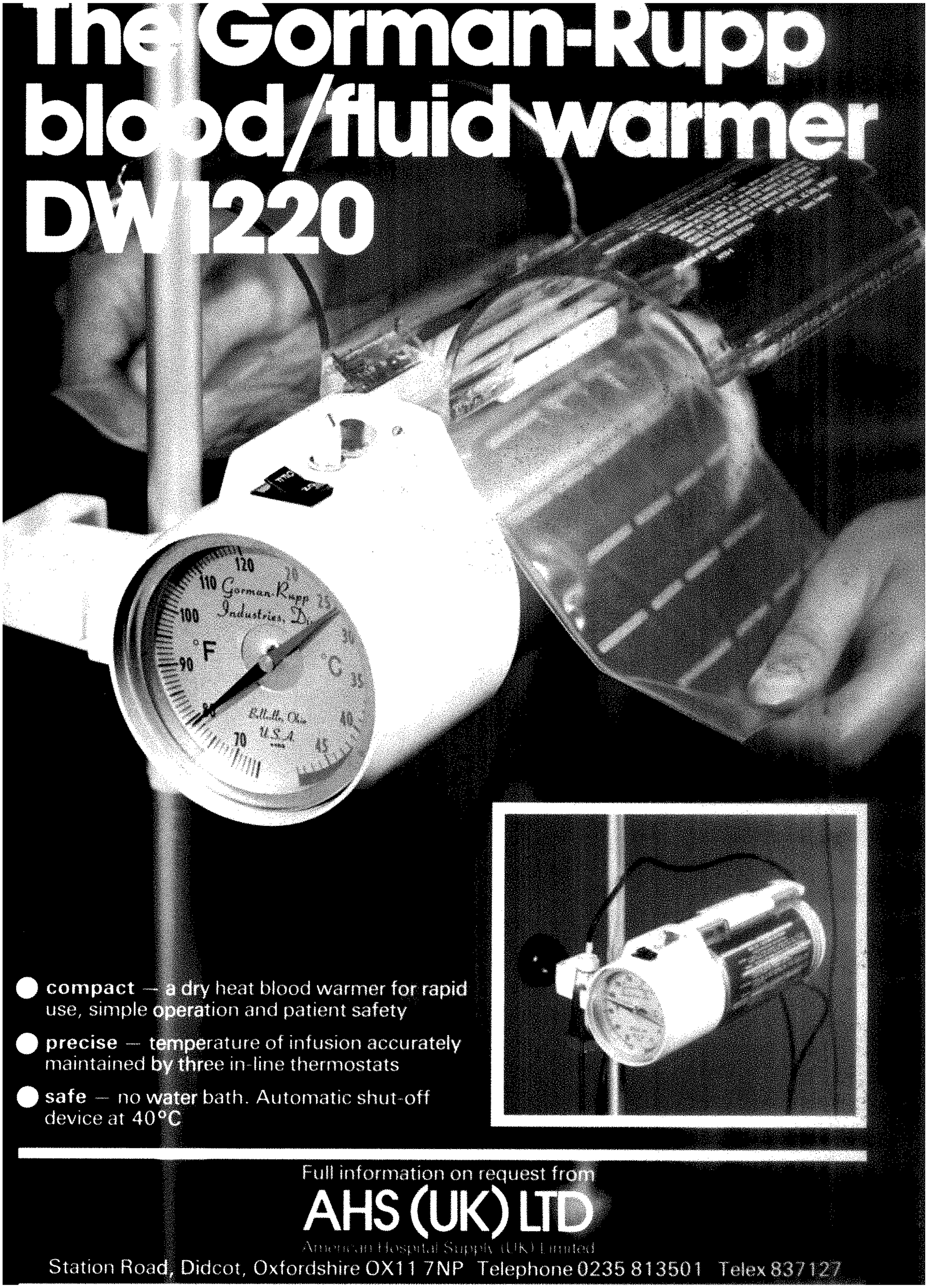
LONG-ACTING

Marcain

bupivacaine hydrochloride BP

DF

The Trade Mark "MARCAIN" is the property of
Aktiebolaget Bofors, Sweden.
DUNCAN FLOCKHART & CO. LIMITED, LONDON E2 6LA.
Further information is available on request.



The Gorman-Rupp blood/fluid warmer DW1220

- **compact** — a dry heat blood warmer for rapid use, simple operation and patient safety
- **precise** — temperature of infusion accurately maintained by three in-line thermostats
- **safe** — no water bath. Automatic shut-off device at 40°C

Full information on request from

AHS (UK) LTD

American Hospital Supply (UK) Limited

Station Road, Didcot, Oxfordshire OX11 7NP Telephone 0235 813501 Telex 837127

You've worked hard for your money

-now let it work hard for you.

Like you, we at Lombard rely on our hard earned skills. Our experience over many years has made us an important name in British Banking and Finance to help people like you make their money grow by depositing with us.

We have a wide range of specially designed Deposit Account Schemes offering sound rates of interest which is paid without deduction of tax at source.

For further details of our deposit facilities and current interest rates without any obligation, simply post the coupon today.

Lombard North Central
Bankers

To:
LOMBARD NORTH CENTRAL LTD,
DEPT. U942,
17 BRUTON STREET,
LONDON W1A 3DH.
Tel: 491 7050

Name:
(BLOCK CAPITALS PLEASE)
Address:

A member of the National Westminster Bank Group whose capital and reserves exceed £1,300,000,000.

FULLY ACCREDITED ANESTHESIA RESIDENCY PROGRAM

PGY-1, 2, 3, and 4

Applications are now being accepted for Anesthesia Residencies, (PGY-1, 2, 3, and 4) in the Department of Anesthesia, University of Massachusetts Medical Center, Worcester, Massachusetts, U.S.A.

The fellowship positions (PGY-4) will be available in the following areas: Cardiac Anesthesia, Regional Anesthesia, S.I.C.U., Intractable Pain and Research.

Interested candidates, please submit curriculum vitae to Michael Stanton-Hicks, M.B.B.S., Program Director of Residency Program, Professor and Chairman, Department of Anesthesia.

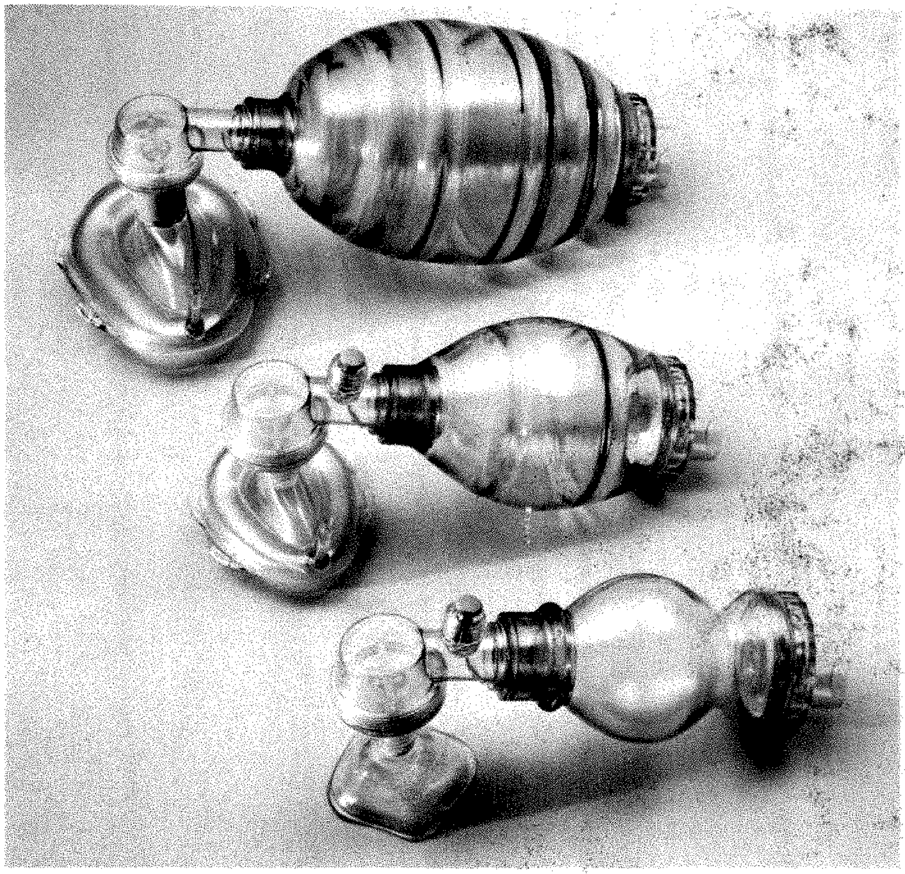
55 Lake Avenue North, Worcester,
MASS. 01605 U.S.A.

University of Massachusetts Medical Center

An Affirmative Action/
Equal Opportunity Employer

Only from Laerdal.

Portable resuscitators for Adults. Children. Infants.



May be used for assisted ventilation (including CPAP and PEEP) oxygen therapy, and anesthesia ventilation in addition to resuscitation. All have Laerdal's NEW right-angled non-rebreathing valve.
Special pressure limiting devices on child and infant models. Also features newly designed masks that insure air tight seal. Available in basic and complete models in different containers for various applications.

LAERDAL

Laerdal Adult Resuscitator. Bag volume of 1800 ml. Mask sizes: 3, 4, 5.

Laerdal Child Resuscitator. Bag volume of 500 ml. Mask sizes: 2, 3.

Laerdal Infant Resuscitator. Bag volume of 240 ml. Mask sizes: 0, 1, 2.

Laerdal HiO$_2$ Kit. Facilitates delivery of 100% oxygen even at a moderate rate of flow.

For more information contact:
Vickers Limited Medical Engineering Priestley Road Basingstoke Hampshire England RG24 9NP
Telephone 0256 29141 Telex 858697

When you require higher pressure and flows...
the MA-2 can be a lifesaver.

When extreme conditions such as status asthmaticus, aspiration pneumonitus, A.R.D.S. and Pickwickian Syndrome require ventilator therapy, you may require higher pressures and flows than are commonly available on most ventilators. Puritan-Bennett has increased the operating range of the MA-2 Volume Ventilator to provide:

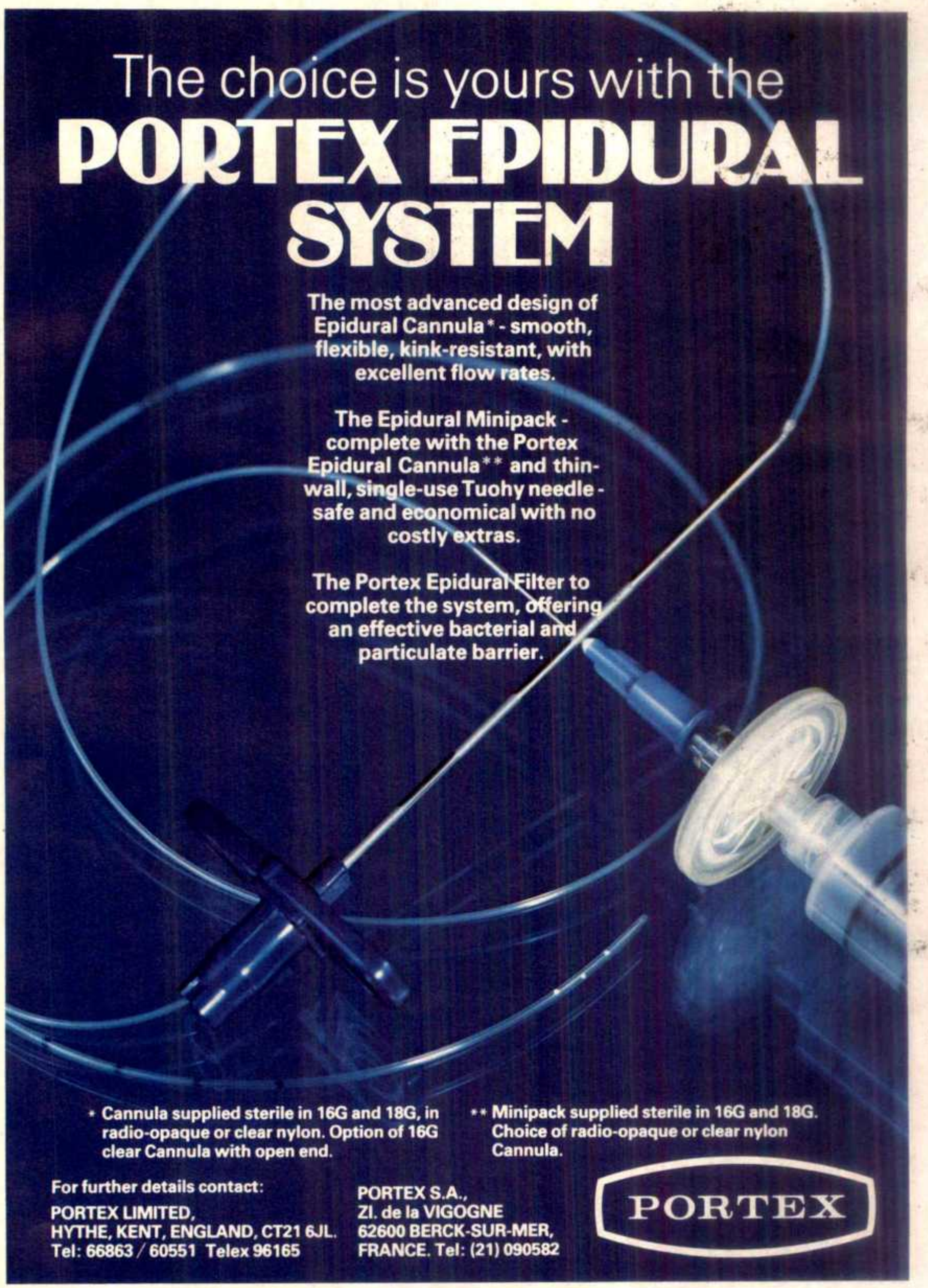
- Adjustable peak system pressures up to 120 cmH_2O
- Adjustable peak flows up to 125 LPM
- Adjustable base line pressures (PEEP/CPAP) up to 45 cmH_2O

Significantly increased performance... an extra capability from Puritan-Bennett.

Puritan-Bennett International Corp.
Bognor Road, Chichester, Sussex PO19 2PH.
Telex: 86462. Cables: Puremade Chichester.
Serving Europe, the Middle-East and Africa.

PURITAN-BENNETT CORPORATION

10th & Harrison, Berkeley, California 94710.
Serving Japan, Australia, the Philippines, India and the Pacific Orient.
7280 N.W. 58th Street, Miami, Florida 33166.
Serving Central America, South America, Mexico and the Caribbean.



The choice is yours with the

PORTEX EPIDURAL SYSTEM

The most advanced design of Epidural Cannula* - smooth, flexible, kink-resistant, with excellent flow rates.

The Epidural Minipack - complete with the Portex Epidural Cannula** and thin-wall, single-use Tuohy needle - safe and economical with no costly extras.

The Portex Epidural Filter to complete the system, offering an effective bacterial and particulate barrier.

* Cannula supplied sterile in 16G and 18G, in radio-opaque or clear nylon. Option of 16G clear Cannula with open end.

** Minipack supplied sterile in 16G and 18G. Choice of radio-opaque or clear nylon Cannula.

For further details contact:

PORTEX LIMITED,
HYTHE, KENT, ENGLAND, CT21 6JL.
Tel: 66863 / 60551 Telex 96165

PORTEX S.A.,
ZI. de la VIGOGNE
62600 BERCK-SUR-MER,
FRANCE. Tel: (21) 090582

PORTEX

DALHOUSIE UNIVERSITY

DEPARTMENT OF ANAESTHESIA

Chief of Service

SAINT JOHN REGIONAL HOSPITAL

The Saint John Regional Hospital, a teaching hospital of the Faculty of Medicine, Dalhousie University, is inviting applications from qualified medical practitioners for the position of Chief of the Department of Anaesthesia.

A new 700-bed hospital, with capacity to expand to 800 plus, is presently under construction to replace the present Regional Hospital in April of 1982.

The hospital is integrated with Dalhousie University for Resident, Interne, and Clinical Clerk training. The Chief of Anaesthesia will be appointed to an appropriate rank in the Faculty of Medicine.

The residential environs of Saint John are most attractive with a full range of educational (including University) and recreational facilities— golf, curling, skiing, sailing, etc.

Submit application with complete curriculum vitae to:

CHAIRMAN OF THE
SELECTION ADVISORY COMMITTEE,
DEPARTMENT OF ANAESTHESIA,
VICTORIA GENERAL HOSPITAL,
HALIFAX, NOVA SCOTIA B3H 2Y9

SURGICAL REPAIR & RECONSTRUCTION IN RHEUMATOID DISEASE

ALEXANDER BENJAMIN & BASIL HELAL.
Basil Helal is Orthopaedic Surgeon at the London Hospital, and Alexander Benjamin is Orthopaedic and Traumatic Surgeon to Peace Memorial Hospital, Watford and West Herts. Hospital.

SUMMER 1980; £25.00; 224pp;
ISBN 0 333 24683 7.

Two orthopaedic surgeons with long experience of the surgical management of rheumatoid disease present in this book an authoritative and balanced account of their approach to this difficult affliction. Among the topics covered are the history, aetiology, pathology and investigation of rheumatoid disease, and the role that surgery has to play in its management. The place of the rheumatoid patient in the family is also discussed.

The role of conservative surgical management is emphasised and placed in proper perspective in relation to the more radical surgery of prosthetic replacement. Prime consideration is given at all times to the needs and interests of the individual patient. Throughout the book much previously unpublished material is presented, both from the authors' work and from that of clinicians in Europe and America.
More than 500 illustrations of the highest quality are included in this book.

M

Scientific and Medical Division, Macmillan Publishers Ltd.,
Houndmills, Basingstoke, Hampshire RG21 2XS.

The Owl Universal System

For all R.F. Lesion Procedures in the Treatment of Pain.

Owl Universal RF System – Model URF-1.

- ☐ **Percutaneous cordotomy**
- ☐ **Trigeminal ganglionotomy**
- ☐ **Facet rhizotomy**
- ☐ **Thalamotomy**
- ☐ **Hypophysectomy**

The complete Radiofrequency Generator for RF Electrocoagulation

The Owl Universal RF System is a quality instrument, safety engineered, that provides an unparalleled combination of features:

- ☐ Radiofrequency lesion generator in two ranges – 5 watts and 25 watts
- ☐ Electrical stimulator with wide range of outputs
- ☐ Impedance monitor
- ☐ Temperature monitor and an ultra-fast responding Temperature Sensing Probe
- ☐ Versatile electronic timer with automatic timing
- ☐ All solid state circuitry for maximum reliability
- ☐ Built-in calibration and test
- ☐ All patient connections electrically isolated for maximum safety
- ☐ Colour coded front panel with illuminated push-button control
- ☐ Simple to use, portable

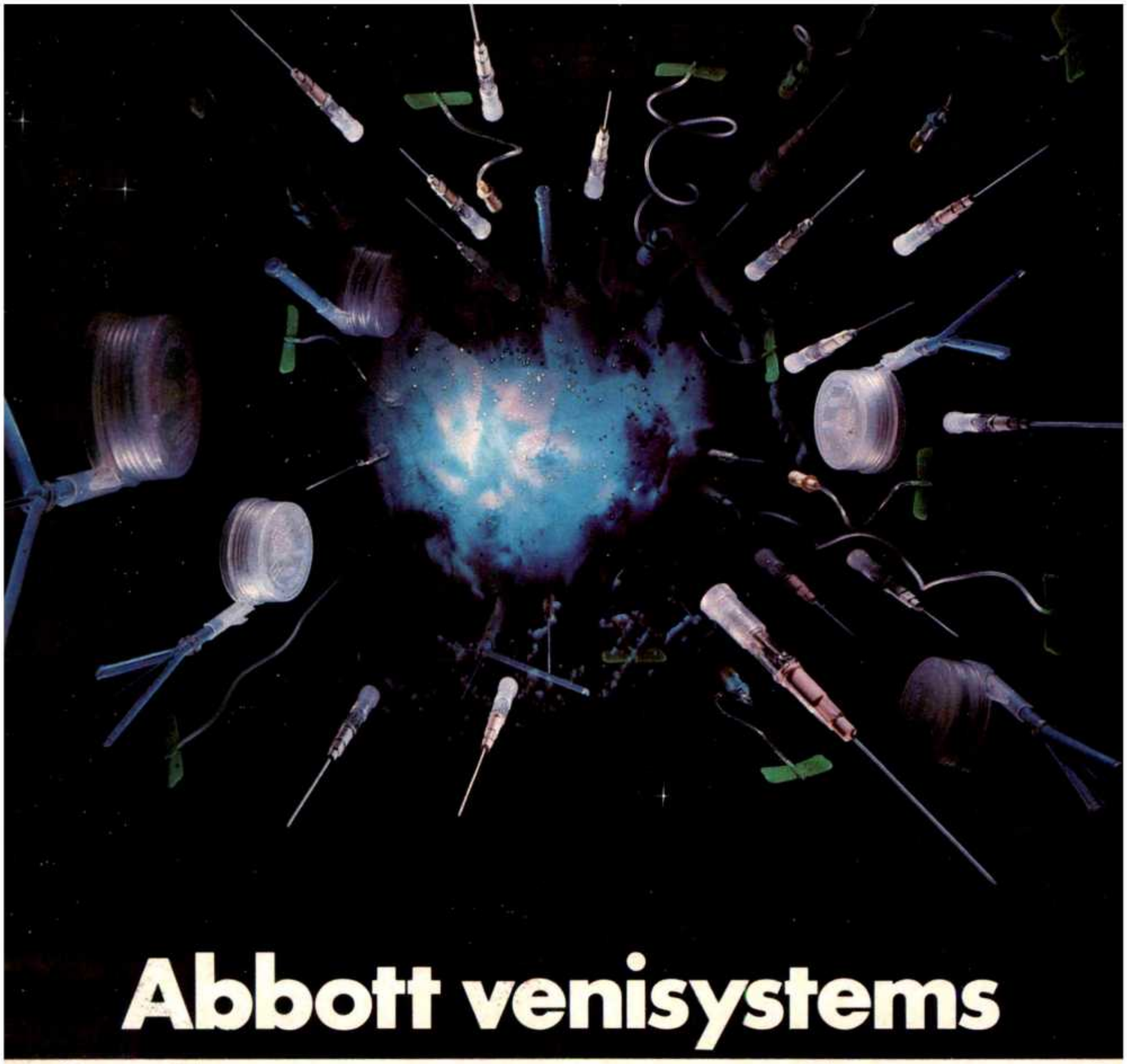
OWL

Downs Surgical

To Downs Surgical Ltd., Church Path, Mitcham, Surrey CR4 3UE, England.
Please send me further details of the Owl Universal System.

Name ____________________

Address ____________________



Abbott venisystems

Light-years ahead

Whatever the venipuncture procedure, you need look no further than the Abbott range.

Meeting the need for all short-term fluid and electrolyte therapies, intermittent drug therapy and renal dialysis is the famous *Butterfly*® range of winged infusion sets – the most comprehensive range of its kind.

For all longer-term fluid and electrolyte therapies, central venous catheterisation and arterial cannulation there s *Abbocath*®*-T* – a full range of FEP Teflon® intravenous cannulae.

And for central venous catheterisation via the peripheral route, there is the unique *Drum-Cartridge*® *catheter.*

Quality venipuncture products from Abbott – for every user need.

Think Venipuncture. Think Abbott.

Please send me further information on the Abbott range of venipuncture products.

Name

Position

Hospital

Further information is available from:
Abbott Laboratories Limited, Queenborough, Kent ME11 5EL

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 6 JUNE 1980

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

EDITORIAL

FENTANYL AND THE METABOLIC RESPONSE TO SURGERY

There has been considerable interest recently in the i.v. administration of large doses of fentanyl during anaesthesia—high dose fentanyl (Editorial, 1979). This term is clearly unsatisfactory as each anaesthetist has his own opinion as to what constitutes a "high" dose of fentanyl. In this editorial the term will be used to mean a dose of at least 50 μg kg^{-1} body weight.

Stanley and colleagues have demonstrated in several studies that high dose fentanyl produces satisfactory anaesthesia for cardiac surgery with good cardiovascular stability. However, most of their experiments have not included other anaesthetic techniques, so that a direct comparison cannot be made (Stanley and Webster, 1978; Lunn et al., 1979; Stanley, Philbin and Coggins, 1979). The busy anaesthetist will require more convincing evidence of any benefits before he is willing to use a technique which many consider to be an expensive method of ensuring respiratory depression in the period after operation. It is likely that, if this technique becomes an accepted part of anaesthetic practice, it will be because of the ability of high dose fentanyl to control some of the endocrine and metabolic responses to surgery (Hall et al., 1978), rather than any improvement in cardiovascular status.

In healthy patients undergoing minor surgery there is little to be gained by inhibiting small and transient metabolic responses, and the possibility of respiratory depression after high dose fentanyl makes this technique both unnecessary and undesirable. During major surgery, however, the metabolic changes are profound. A reduction in the excessive mobilization of substrates such as glucose and non-esterified fatty acids is beneficial, and usually reflects an improvement in the severe endocrine disturbance.

The metabolic and hormonal changes found during surgery have been well documented, but the precise cause remains unknown. Afferent sensory impulses from the injured area are obviously important, but other factors, such as changes in blood volume, may also be implicated. Among the methods used to try to reduce or prevent the metabolic response to surgery are extradural or spinal analgesia and large doses of i.v. analgesics.

Engquist and others (1977) showed that extradural blockade from T4 to S5 was necessary to inhibit completely the cortisol and glucose response to hysterectomy. They also demonstrated that maintenance of analgesia at T4–S5 for the first 24 h after operation was associated with an improvement in nitrogen balance (Kehlet, 1978) and a reduction in perioperative granulocytosis and lymphopenia (Rem, Brandt and Kehlet, 1980). Unfortunately, extradural analgesia is much less effective in abolishing the metabolic response to upper abdominal and thoracic surgery. Bromage, Shibata and Willoughby (1971) found that, although the glycaemic response was markedly decreased by thoracic extradural analgesia, there was no effect on the cortisol response. They postulated that extradural blockade of sympathetic efferent fibres prevented hyperglycaemia, whereas the hormonal changes were the result of stimulation of vagal afferent fibres and thus unresponsive to extradural block. If this interpretation is correct, local analgesic techniques allow complete control of the metabolic response only in pelvic and limb surgery.

The use of i.v. morphine to control the metabolic response to surgery was investigated by George and colleagues (1974). They observed that morphine 1 mg

kg^{-1} body weight reduced the cortisol response to abdominal surgery and that morphine 4 mg kg^{-1} body weight abolished the cortisol and growth hormone response to cardiac surgery until cardiopulmonary bypass. The cardiovascular difficulties produced by the administration of morphine 4 mg kg^{-1} body weight were exemplified in a study by Brandt and others (1978) who found it necessary to give the morphine in divided doses over 30–60 min. Fentanyl, with its cardiovascular stability and shorter duration of action, offers important advantages over morphine and Hall and others (1978) showed that fentanyl 50 $\mu g\ kg^{-1}$ body weight abolished the cortisol, growth hormone and glucose response to prolonged pelvic surgery.

It remains to be determined whether high dose fentanyl will prevent or reduce the hormonal and metabolic response to more severe surgical trauma. Preliminary findings at Hammersmith Hospital suggest that various high dose fentanyl regimens are effective in upper abdominal and cardiac surgery. The recent results of Stanley and others (1979) show that fentanyl 50–100 $\mu g\ kg^{-1}$ body weight produced a considerable reduction in the cortisol response to cardiopulmonary bypass. These initial observations require confirmation, but it is likely that the high dose fentanyl technique will be effective in operations in which extradural analgesia is of little value in reducing the metabolic changes. Large doses of other potent analgesics with pure agonist effects will probably have actions similar to fentanyl and morphine.

There are no studies in which the effects of fentanyl on the metabolic and hormonal changes during surgery have been continued into the period after operation. Thus it is not known if this technique produces any long-term metabolic benefits for the patient, such as a reduction in the loss of muscle protein. It is possible that high dose fentanyl merely delays the response by several hours to the period after operation, although it is doubtful if the changes are then so severe.

The role of analgesia after surgery in reducing the metabolic and hormonal response has also not been investigated. However, it can be argued from the data of Bromage, Shibata and Willoughby (1971) that, after upper abdominal and thoracic surgery, the provision of adequate analgesia will have little metabolic effect because of the importance of vagal afferent activity in stimulating the endocrine response.

There are, therefore, many aspects of the high dose fentanyl technique which need further study, but the ultimate goal of an anaesthetic technique which favourably influences the metabolic response to surgery merits intensive investigation.

G. M. Hall

REFERENCES

Brandt, M. R., Korshin, J., Prange Hensen, A., Hummer, L., Nistrup Madsen, S., Rygg, I., and Kehlet, H. (1978). Influence of morphine anaesthesia on the endocrine–metabolic response to open-heart surgery. *Acta Anaesthesiol. Scand.*, **22**, 400.

Bromage, P. R., Shibata, H. R., and Willoughby, H. W. (1971). Influence of prolonged epidural blockade on blood sugar and cortisol responses to operation upon the upper part of the abdomen and thorax. *Surg. Gynaecol. Obstet.*, **132**, 1051.

Editorial (1979). High-dose fentanyl. *Lancet*, **1**, 81.

Engquist, A., Brandt, M. R., Fernandes, A., and Kehlet, H. (1977). The blocking effect of epidural analgesia on the adrenocortical and hyperglycaemic responses to surgery. *Acta Anaesthesiol. Scand.*, **21**, 330.

George, J. M., Reier, C. E., Lanese, R. R., and Rower, J. M. (1974). Morphine anaesthesia blocks cortisol and growth hormone response to surgical stress in humans. *J. Clin. Endocrinol. Metab.*, **38**, 736.

Hall, G. M., Young, C., Holdcroft, A., and Alaghband-Zadeh, J. (1978). Substrate mobilisation during surgery. A comparison between halothane and fentanyl anaesthesia. *Anaesthesia*, **33**, 924.

Kehlet, H. (1978). The influence of epidural analgesia on the endocrine–metabolic response to surgery. *Acta Anaesthesiol. Scand.* (Suppl.) **70**, 39.

Lunn, J. K., Stanley, T. H., Eisele, J., Webster, L., and Woodward, A. (1979). High dose fentanyl anesthesia for coronary artery surgery: Plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. *Anesth. Analg.* (*Cleve.*), **58**, 390.

Rem, J., Brandt, M. R., and Kehlet, H. (1980). Prevention of postoperative lymphopenia and granulocytosis by epidural analgesia. *Lancet*, **1**, 283.

Stanley, T. H., Berman, L., Green, O., Robertson, D. H., and Roizen, L. (1979). Fentanyl–oxygen anesthesia for coronary artery surgery: plasma catecholamine and cortisol responses. *Anesthesiology*, **51**, S139.

—— Philbin, D. M., and Coggins, C. H. (1979). Fentanyl–oxygen anaesthesia for coronary artery surgery: Cardiovascular and antidiuretic hormone responses. *Can. Anaesth. Soc. J.*, **26**, 168.

—— Webster, L. R. (1978). Anaesthetic requirements and cardiovascular effects of fentanyl–oxygen and fentanyl–diazepam–oxygen anesthesia in man. *Anesth. Analg.* (*Cleve.*), **57**, 411.

Br. J. Anaesth. (1980), **52**, 563

CHANGES OF THE CELL BODIES IN THE FACIAL NUCLEUS AFTER FACIAL NERVE BLOCK

T. Totoki, K. Harano, Y. Aika and T. Kanaseki

SUMMARY

Facial nerve blocks were produced in four monkeys by insertion of a needle into the facial nerve trunk. The sequential changes of nerve cells in the facial nucleus were investigated 4 days, and 2 and 7 months later. Although the facial paralysis recovered in 2 months, considerable changes of cell bodies in the facial nucleus were still obvious which recovered completely only after 7 months. It is postulated that an optimum discharge is generated by those nerve cells in the facial nucleus during the recovery period which in clinical practice could result in 6 months of clinical remission from facial spasm.

Physical nerve-block (insertion of a needle directly to the bony facial canal to damage the nerve) developed by Wakasugi (1972a, b) has been regarded as the most effective treatment for facial spasm. Using this method we have treated 225 patients with hemifacial spasm in the Pain Clinic of Kyushu University Hospital. When the nerve block was applied, the spasm disappeared immediately. The facial paralysis which developed then recovered gradually in 1.5–2 months (fig. 1). Thereafter, the patients were symptom-free for about 6 months without any paralysis or spasm. However, relapse occurred in many cases within 8–10 months after treatment (fig. 2). Stimulated by these clinical observations, we observed the changes in the nerve cells of the facial nucleus following nerve block in Japanese monkeys.

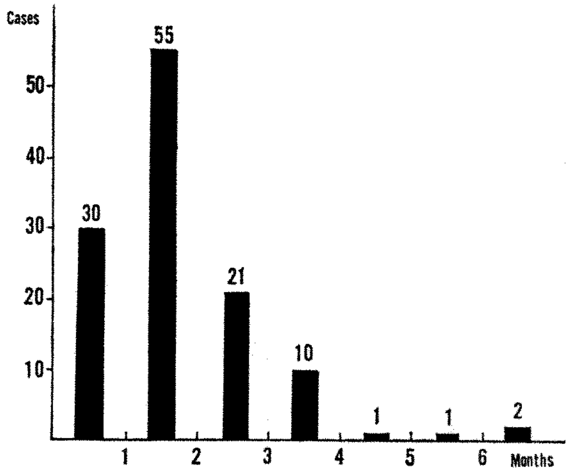


FIG. 1. Time required for the paralysis to recover after facial nerve block.

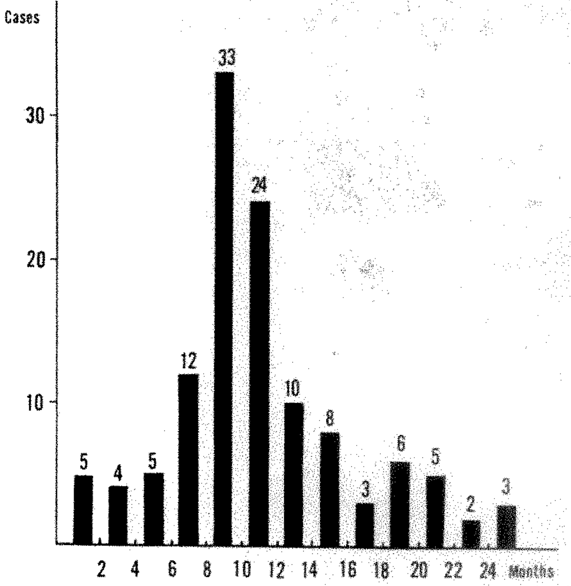


FIG. 2. Period of remission after facial nerve block before relapse.

METHODS AND HISTOLOGICAL PROCEDURES

Four male Japanese monkeys (4–10 yr old) were studied. Three of them were anaesthetized with ketamine hydrochloride, and a 22-gauge needle was inserted into the neural canal of the facial nerve to produce a nerve block (fig. 3). The needle was

---

Tadahide Totoki, M.D.; Kiyoshi Harano, M.D. D.M.SCI.; Department of Anaesthetics, Kyushu University, School of Medicine, Fukuoka, Japan; Yusuke Aika, M.S.; Takeshi Kanaseki; M.D., D.M.SCI.; Department of Anatomy, Kyushu University, School of Medicine, Fukuoka, Japan.

0007–0912/80/060563–04 $01.00

© Macmillan Journals Ltd 1980

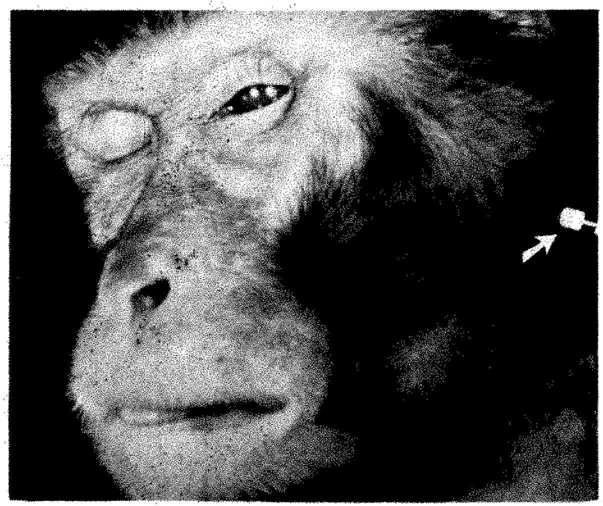


FIG. 3. Facial nerve block in a Japanese monkey. The needle is inserted about 5 mm below the tip of the stylomastoid process, and moved parallel to the frontal plane at 30° to the sagittal plane to reach the stylomastoid foramen. The peripheral facial nerve becomes paralysed when the needle (arrow) enters the neural canal. The animal is unable to close its eye and the cornea is exposed by about 3 mm; a prominent angular paralysis is evident.

removed 30 min later after producing complete paralysis. One monkey was used as control. The animals were deeply anaesthetized and the tissues fixed by intracardiac perfusion with 10% formalin 5 litre at 4 days, and at 2 and 7 months after the nerve block. The brain was removed immediately, fixed in 99% alcohol and immersed in celloidin. The brain stem was cut serially in 30-μm sections in the transverse plane and stained with toluidine blue.

RESULTS

Normal characteristics of the facial nucleus in a 6-yr-old monkey weighing 12 kg

The facial nucleus was found as a group of neurons symmetrically located on the ventrolateral side of the abducens nucleus at the lower edge of the pons. This group of neurons appeared nearly circular in cross-section, and could be identified distinctly from the surrounding tissues. The nerve cells were stellate, spindly, or oval, with a single nucleus located mostly in the centre of the cell body. The nuclear membrane was prominent and the Nissl's granules were lined along the perimeter of the cells with a thick concentration around the outer edge of the nuclei (fig. 4: 1).

Experimental monkeys

(1) *A 5-yr-old monkey weighing 11.6 kg. Sacrificed 4 days after nerve block.* The facial nerve of the blocked side was completely paralysed. The animal was unable to close its eye, with the cornea exposed by about 3 mm, and was unable to drink water from the water bottle because of angular paralysis. The nerve cells of the facial nucleus were circular with the nuclei shifted to one side of the cells. Dispersion of the Nissl substance, with decrease in size of the Nissl granules, was present in the neurons (fig. 4: 2).

(2) *A 10-yr-old monkey weighing 16 kg. Sacrificed at 2 months after nerve block.* The facial paralysis of the blocked side had almost completely recovered except that the nictitating reflex was slightly slower than on the normal side. In the facial nerve cells, basophil granules had reappeared next to the nuclear membrane. However, the granules were still small and the nuclei were positioned towards one side of the cells. No normal cell was found (fig. 4: 3).

(3) *A 4-yr-old monkey weighing 9 kg. Sacrificed at 7 months after nerve block.* No difference was visible between the blocked and unblocked sides of the face. The nerve cells in the facial nucleus were nearly normal in the blocked side, but an incomplete picture of recovery with the presence of small Nissl's granules was observed in some cells (fig. 4: 4).

In the nerve-blocked animals, no difference in the number of nerve cells of the nucleus was evident between the blocked and unblocked sides.

DISCUSSION

Because the aetiology of idiopathic hemifacial spasm has remained unknown, no causative agent or reliable treatment has been established. Facial nerve block by alcohol injection (Harris and Wright, 1932), neuroanastomosis (Törmä, 1962) and neurotomy have been reported to be valuable procedures to control the condition. Alcohol injection and neuroanastomosis reduce hyperexcitability of the facial nerve by producing a pronounced facial palsy. The partial division of the facial nerve either at the peripheral branches (Diamant, Enfors and Wiberg, 1967) or at the major branches (Scoville, 1969) may result in severe facial palsy. The recently reported effect of facial nerve decompression at the cerebellopontine angle requires further evaluation (Jannetta et al., 1977).

The facial nerve block method developed by Wakasugi (1972a) has been regarded as the most effective therapy for facial spasm, and many reports have supported this (Wakasugi, 1972a, b). However,

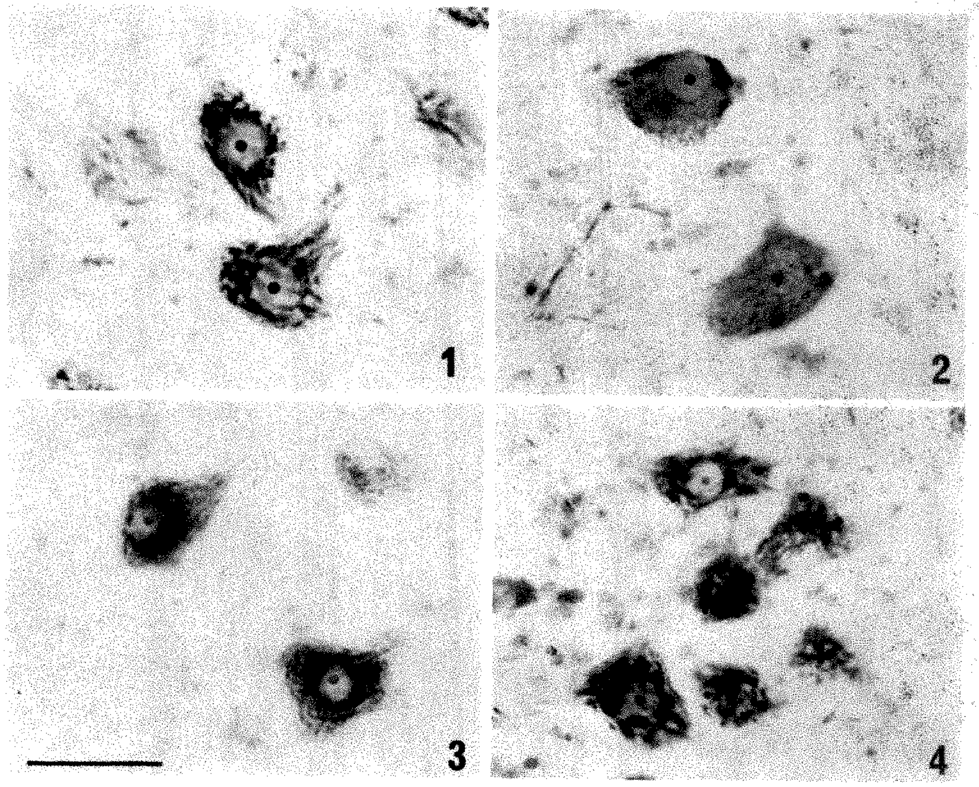


FIG. 4. Cells of the facial nucleus: 1 = normal facial nucleus; 2 = 4 days after nerve block; 3 = 2 months after nerve block; 4 = 7 months after nerve block. Nissl stain. Horizontal bar = 50 μm.

the mechanism of production of a long remission following paralysis remained unknown. This study attempted to clarify changes occurring in the nerve cells at the facial nucleus.

It is known that when the axon of a nerve cell is injured, sequential changes are produced in the body of the cell. According to Geist (1933), these changes vary depending on the following factors; (1) species, (2) age, (3) distance between the point of injury and nerve cell, (4) period of survival after operation and (5) the histological and functional type of neuron. This study was conducted using the same clinical procedure to produce a facial nerve block in mature monkeys which are considered to be anatomically close to man. The period of investigation was intended to cover the 2-month period when paralysis disappears and the 7-month period when relapse of spasm occurs. The sequence of recovery of facial paralysis after a nerve block in monkeys was about the same as that in man.

Nissl (1891) first observed a degenerative change in the nerve cells of the facial nucleus after the facial nerve was severed. A more detailed study was conducted by Cammermeyer (1955, 1963a, b, 1969). However, these studies were concerned with the consequences of cutting the facial nerve below the stylomastoid foramen and no observation was made on changes produced in the nerve by inserting a needle into the neural canal.

Torvik and Skjörten (1971) investigated the degenerative changes produced in nerve cells following crushing of the facial nerve of mice close to the stylomastoid foramen. According to their report, the nerve function of the animals recovered in 10–12 days, but it required 30–60 days for complete recovery of the central nervous system. It was also confirmed in our experiments that the nerve function recovered in 2 months but that it took 7 months for the nerve cells in the facial nerve nucleus to recover completely. On the basis of these observations, the mechanism by which a complete remission for about 6 months is produced in patients following nerve block is suggested. During this period of remission the nerve cells in the facial nucleus are in the process of recovery and generate an optimum discharge to the peripheral nerves to produce a clinically normal state. The return of facial spasm which occurred about 8 months after the block may be a consequence of complete recovery of the nerve cells.

REFERENCES

Cammermeyer, J. (1955). Astroglial changes during retrograde atrophy of nucleus facialis in mice. *J. Comp. Neur.*, **102**, 133.

—— (1963a). Peripheral chromatolysis after transection of mouse facial nerve. *Acta Neuropathol. (Berl.)*, **2**, 213.

—— (1963b). Differential response of two neuron types to facial nerve transection in young and old rabbits. *J. Neuropathol. Exp. Neur.*, **22**, 594.

—— (1969). Species differences in acute retrograde neuronal reaction of the facial and hypoglossal nuclei. *J. Hirnforsch.*, **11**, 13.

Diamant, H., Enfors, B., and Wiberg, A. (1967). Facial spasm. *Laryngoscope*, **77**, 350.

Geist, F. D. (1933). Chromatolysis of efferent neurons. *Arch. Neur. Psychiatr. (Chicago)*, **29**, 88.

Harris, W., and Wright, A. D. (1932). Treatment of clonic facial spasm. *Lancet*, **1**, 657.

Jannetta, P. J., Abbasy, M., Maroon, J. C., Ramos, F. M., and Albin, M. S. (1977). Etiology and definitive microsurgical treatment of hemifacial spasm. *J. Neurosurg.*, **47**, 321.

Nissl, F. (1891). Ueber die Veränderungen der Ganglienzellen am Facialiskern des Kaninchens nach Ausreissung der Nerven. *Allg. Z. Psychiat.*, **48**, 197.

Scoville, W. B. (1969). Partial extracranial section of seventh nerve for hemifacial spasm. *J. Neurosurg.*, **31**, 106.

Törmä, T. (1962). Experience in the treatment of paroxysmal hemifacial spasm. *Acta Neurol. Scand.*, **38**, 217.

Torvik, A., and Skjörten, F. (1971). Electron microscopic observations on nerve cell regeneration and degeneration after axon lesions. *Acta Neuropathol. (Berl.)*, **17**, 248.

Wakasugi, B. (1972a). Facial nerve block in the treatment of facial spasm. *Arch Otolaryngol.*, **95**, 356.

—— (1972b). Hemifacial spasm—Review of 2300 cases. *Jap. Med. J.*, **2535**, 26.

MODIFICATIONS DES CORPS DE CELLULES DU NOYAU FACIAL APRES BLOCAGE DU NERF DE LA FACE

RESUME

On a provoqué le blocage du nerf de la face sur quatre singes, en insérant une aiguille dans le tronc du nerf facial. On a étudié les modifications continues qui se sont produites dans les cellules du nerf du noyau facial: 4 jours plus tard, de même que 2 mois et 7 mois après. Bien qu'ils se soient remis de la paralysie faciale en deux mois, on pouvait toujours voir que des changements considérables s'étaient produits dans les corps de cellules du noyau facial, et dont ils ne se sont complètement remis qu'après sept mois. On considère qu'il est possible qu'une décharge optimale soit produite par ces cellules nerveuses du noyau facial pendant la période de récupération laquelle, dans la pratique clinique, pourrait entraîner une remission clinique des spasmes faciaux en six mois.

ZELLKÖRPERVERÄNDERUNGEN IM GESICHTSNUKLEUS NACH GESICHTSNERVBLOCKIERUNG

ZUSAMMENFASSUNG

Der Gesichtsnerv von 4 Affen wurde durch Einführung einer Nadel in den Gesichtsnervenstamm blockiert. Die sich ergebenden Nervenzellenveränderungen im Gesichtsnukleus wurden nach 4 Tagen sowie nach 2 und 7 Monaten untersucht. Obwohl die Gesichtslähmung nach 2 Monaten vorüber war, waren immer noch wesentliche Veränderungen der Zellkörper im Gesichtsnukleus erkennbar, die erst nach 7 Monaten völlig verschwanden. Es wird gefolgert, dass während der Erholungsperiode eine optimale Entladung dieser Nervenzellen im Gesichtsnukleus stattfindet, was in der klinischen Praxis zu einer sechsmonatigen Remission von Gesichts krämpfen führen könnte.

CAMBIOS DE LOS CUERPOS CELULARES EN EL NUCLEO FACIAL DESPUES DEL BLOQUEO DEL NERVIO FACIAL

SUMARIO

Se provocaron bloqueos del nervio facial de cuatro monos mediante la inserción de una aguja en el tronco del nervio facial. Los cambios consecuentes de las células del nervio en el núcleo facial fueron objeto de investigaciones 4 días, y 2 y 7 meses después. Aunque se repusieron en 2 meses de la parálisis facial, eran evidentes aún considerables cambios de los cuerpos celulares en el núcleo facial, los que se recuperaron totalmente 7 meses después solamente. Se da por sentado que una descarga óptima es causada por esas células nerviosas en el núcleo facial en el curso del período de recuperación, el cual podría, en práctica clínica, resultar en una remisión clínica de 6 meses en cuanto al espasmo facial.

Br. J. Anaesth. (1980), **52**, 567

PROTECTIVE EFFECT OF STEROIDS ON CULTURED CELLS DAMAGED BY HIGH CONCENTRATIONS OF OXYGEN

J. E. STURROCK AND G. H. HULANDS

SUMMARY

Chromosomal aberrations resulting from the exposure of Chinese hamster lung fibroblast cells to 95% oxygen have been used to investigate the protective effect of three steroids. Hydrocortisone had little useful effect. However, dosage of both methylprednisolone and dexamethasone could be increased to a level at which damage by oxygen was reduced to 50% of nuclei compared with 90% damaged in cells unprotected by steroids. There was no appreciable impairment of cell growth. Concentrations of steroids required for this effect were respectively 100 and 10 μmol $litre^{-1}$, which corresponds to the high dosage regimen currently used to protect the lungs against the effects of endotoxic shock, haemorrhage and other conditions. The steroids did not protect against the depression of cell growth caused by 95% oxygen.

As long ago as 1899 it was discovered by Lorrain Smith that exposure to a high concentration of oxygen is toxic to pulmonary tissue. However, in cardiopulmonary disease high concentrations are often required to maintain adequate tissue oxygenation and in some instances this causes an exacerbation of the disease with increased mortality. Various mechanisms leading to cell damage have been suggested, ranging from the biochemical (Haugaard, 1968) to the physicochemical (Swartz, 1973), but no single factor has been universally accepted.

Changes in lung morphology after exposure to high oxygen concentrations have been well documented (Kaplan et al., 1969; Weibel, 1971; Kapanci et al., 1972) and there has been much work on the effects of oxygen on cultured cells *in vitro*. Reduction in cell growth has been described (Rueckert and Mueller, 1960; Brosemer and Rutter, 1961; Pace, Thompson and van Camp, 1962; Allison, 1965; Goetz, 1975; Balin et al., 1976) and also a lower cell survival has been found (Rueckert and Mueller, 1960; Sturrock and Nunn, 1978). There are several reports of alterations in cell metabolism during exposure to oxygen (Rueckert and Mueller, 1960; Brosemer and Rutter, 1961; Haugaard, 1965) and damage to chromosomes has also been observed (Conger and Fairchild, 1952; Sturrock and Nunn, 1978).

Exposure of cultured cells to high oxygen concentrations was found to release lysosomal enzymes (Allison, 1965; Gnanadurai et al., 1978), and steroids have been shown to stabilize lysosomal membranes (Weissmann, 1964). We have undertaken experiments using various concentrations of three different steroids to determine if these drugs protect against the damage to chromosomes caused by high concentrations of oxygen *in vitro*.

METHODS

Materials

The steroids tested were methylprednisolone sodium succinate (Upjohn), dexamethasone sodium phosphate (Merck, Sharp and Dohme) and hydrocortisone sodium succinate (Organon). Sodium succinate and sodium phosphate were tested also.

The dose to the cells may be approximately related to clinical dose on the basis of the molecular weights of the three steroids, being very close to 500 mol and an average man of 70 kg having a total of 50 litre of body fluid. Thus 1 μmol $litre^{-1} \simeq$ 0.5 mg $litre^{-1} \simeq$ 25 mg total dose for an average man (0.36 mg kg^{-1}). Equivalent therapeutic doses for the three steroids used in this study are: hydrocortisone 20 mg; methylprednisolone 4 mg; dexamethasone 0.75 mg (Martindale, 1977). The greater doses used in this study correspond to the high dosage regimen (e.g. 30 mg kg^{-1}) of methylprednisolone recommended for protection against the pulmonary complications of septic shock (Schumer, 1976).

Treatment of cultures

The method of growing the Chinese hamster lung fibroblast cells (V.79) has been described previously

---

J. E. STURROCK, M.PHIL.; G. H. HULANDS, M.B., CH.B., F.F.A.R.C.S.; Division of Anaesthesia, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ.

0007-0912/80/060567-06 $01.00

© Macmillan Journals Ltd 1980

(Sturrock and Nunn, 1978). Slides and Petri dishes were treated in four different ways:

(1) Saline added, exposed to air + 5% carbon dioxide (control).
(2) Steroid added, exposed to air + 5% carbon dioxide.
(3) Saline added, exposed to 95% oxygen + 5% carbon dioxide.
(4) Steroid added, exposed to 95% oxygen + 5% carbon dioxide.

Saline or steroid remained in the dishes throughout the experiment.

Chromosome studies

Chinese hamster lung fibroblast cells were grown overnight as a monolayer on glass microscope slides lying in plastic Petri dishes (Sterilin). The medium in the dishes was Eagle's Minimum Essential Medium (Flow Labs) with added glutamine, antibiotics and 10% fetal calf serum (Gibco Biocult). After overnight growth in an incubator at 37 °C in an atmosphere of air with 5% carbon dioxide the dishes were put into desiccators in a hot room at 37 °C for exposure either to 95% oxygen or to air, both gases combined with 5% carbon dioxide. The steroid to be tested was dissolved in saline to the required concentration and sterilized by filtration. This solution was then added to the medium in the dishes, at 1% or 2% v/v of the liquid contained in each dish, 2 h before the cells were exposed to the gas. A similar volume of saline was added to all dishes not receiving steroid. The gas was humidified and passed into the desiccators for 1 h and the effluent gas was monitored with a Servomex paramagnetic oxygen analyser. The desiccators were closed with taps and remained in the hot room for 24 h, after which time the gas in each desiccator was sampled and the slides with their attached cells were removed. Two-thirds of the number of slides were treated with hypotonic saline to expand the cells and separate the chromosomes in the metaphase nuclei and then fixed in ethanol/acid. The remaining slides were fixed without hypotonic treatment and all were stained with 2% Orcein. Fifty consecutive well-spread metaphase nuclei on each slide were examined under the microscope using a × 100 phase-contrast objective.

Growth rate

Cells were grown as before, but on the bottom of plastic Petri dishes without slides. The cells remained in the desiccators in the hot room for 24, 48 or 72 h. Each desiccator was replenished with air or oxygen every 24 h and the gas was sampled before opening it at the end of the exposure. Cells were collected from the dishes with trypsin, diluted and counted in a haemocytometer at 0, 24, 48 or 72 h of exposure to oxygen. Growth rate was calculated as a percentage of control growth rate.

RESULTS

Chromosome aberrations

As reported previously (Sturrock and Nunn, 1978) exposure of Chinese hamster cells to 95% oxygen for 24 h caused about 90% of nuclei to show chromosome aberrations, with usually more than one aberration per nucleus (fig. 1A). Aberrations were mostly gaps or breaks, or both, in one or both chromatids of a pair and there were a few interchanges. Damage was rarely seen in the nuclei of untreated controls (fig. 1B) where the mean frequency of damaged nuclei was 0.67% ($n = 4$, SEM = 0.84).

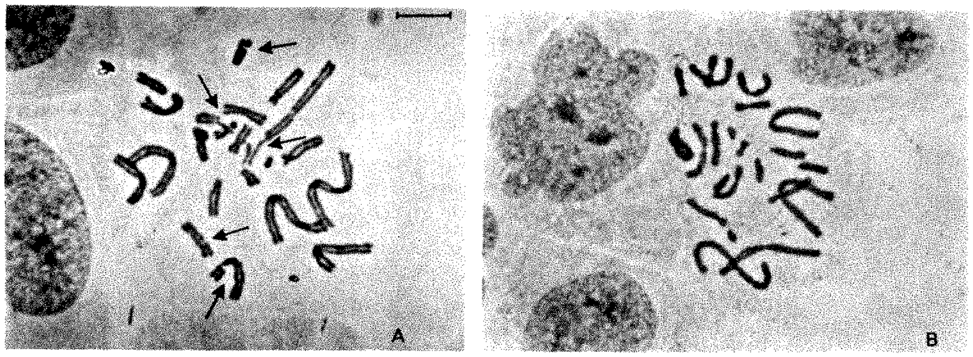


FIG. 1. A: Stained metaphase nucleus (treated with hypotonic saline) showing damage (arrows) to chromatids resulting from exposure to 95% oxygen for 24 h. B: Control, cells grown in air under similar conditions. Bar represents 10 μm.

Cells treated with steroids but exposed to air showed a frequency of between 1% and 1.5% damage after exposure to methylprednisolone 100 μmol litre^{-1} or to dexamethasone or hydrocortisone 10 μmol litre^{-1}.

Steroids caused a dose-related reduction in the frequency of damaged nuclei, but the dose–response curve (fig. 2) was shallow and an appreciable effect was only obtained in the greater dose range. The dotted line in figure 2 shows the mean level of damage caused by exposure for 24 h to 95% oxygen in cells not treated with steroids: mean = 90.1%, 2 SEM ± 1.02, $n = 12$. Significant differences from untreated cells were obtained at the following concentrations and greater: hydrocortisone 1.0 μmol litre^{-1}; methylprednisolone 0.1 μmol litre^{-1}; dexamethasone 0.01 μmol litre^{-1}.

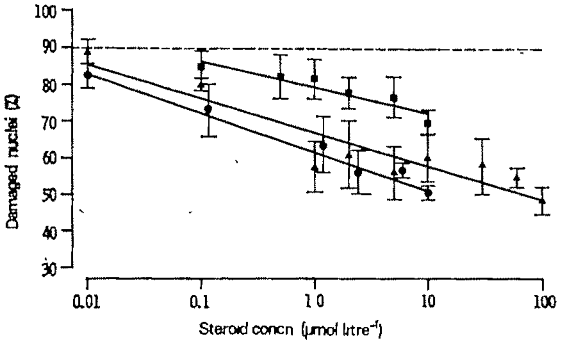


FIG. 2. Calculated regression lines showing dose/response relationships for three steroids which reduced the percentage of nuclei damaged by 24 h treatment with 95% oxygen. The broken line indicates the percentage damaged by 95% oxygen when steroids were not used. Each point represents mean (±2 SEM) for four slides on each of which 50 nuclei were examined. The difference of slope between each of the three steroid regression lines and the 95% oxygen line was significant ($P = 0.001$) ■ = hydrocortisone; ▲ = methylprednisolone; ● = dexamethasone. For all three steroids 1 μmol litre^{-1} ≏ 0.5 mg litre^{-1}.

The number of damaged nuclei was reduced from 90% to 50% after addition of methylprednisolone 100 μmol litre^{-1} or dexamethasone 10 μmol litre^{-1}. Hydrocortisone, in the presence of 95% oxygen, caused severe interference with cell division at concentrations greater than 10 μmol litre^{-1} and there were insufficient mitoses to investigate the drug in the upper dose range where it might have had an appreciable protective effect. Sodium phosphate 2 μmol litre^{-1} (90% damage) or sodium succinate 2 μmol litre^{-1} (87% damage) did not protect chromosomes against 95% oxygen.

Growth rate

Figure 3 shows the effect of methylprednisolone on the growth of cells in culture exposed to air with 5% carbon dioxide for 4 days. Arrow A points to an equivalent clinical dose of about 1–2 mg kg^{-1}, while arrow B points to an equivalent dose of 30 mg kg^{-1}. It can be seen that even the high dose (B) of methylprednisolone reduces cell growth rate only to about 86% of control values, even after 4 days exposure.

Table I shows growth rate for cells exposed to air or to 95% oxygen (both gases with added 5% carbon dioxide) and treated with either methylprednisolone, dexamethasone or hydrocortisone, at high doses

TABLE I. *Growth rates of cells as a percentage of control rates. Cells grown in medium containing either hydrocortisone 10 μmol litre^{-1}, methylprednisolone 60 μmol litre^{-1} or dexamethasone 5 μmol litre^{-1}, and exposed to air or to 95% oxygen for 24, 48 or 72 h. SEM in parentheses*

		Mean cell growth rate % control		
Steroid added	Gas phase	24 h	48 h	72 h
Hydrocortisone				
10 μmol litre^{-1}	Air + 5% CO_2	96.7 (5.1)	100.3 (0.6)	96.5 (1.0)
10 μmol litre^{-1}	95% O_2 + 5% CO_2	39.2 (4.8)	16.0 (2.5)	9.8 (3.6)
No steroid	95% O_2 + 5% CO_2	39.7 (3.1)	17.9 (1.5)	−0.1 (2.0)
Methylprednisolone				
60 μmol litre^{-1}	Air + 5% CO_2	94.9 (2.0)	103.0 (1.8)	95.6 (1.3)
60 μmol litre^{-1}	95% O_2 + 5% CO_2	42.5 (1.0)	20.4 (3.2)	0.6 (1.4)
No steroid	95% O_2 + 5% CO_2	41.8 (1.8)	21.7 (2.6)	−5.3 (1.4)
Dexamethasone				
5 μmol litre^{-1}	Air + 5% CO_2	99.5 (2.0)	97.3 (2.7)	98.5 (1.4)
5 μmol litre^{-1}	95% O_2 + 5% CO_2	42.9 (1.8)	20.0 (2.3)	5.8 (4.0)
No steroid	95% O_2 + 5% CO_2	45.0 (3.2)	23.3 (1.3)	3.4 (2.3)

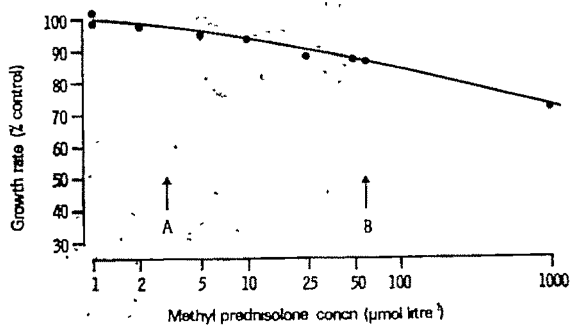


FIG. 3. Growth rate of cells, as percentage of control, in medium containing graded doses of methylprednisolone in air for 4 days. Arrow A shows an equivalent clinical dose of 1–2 mg kg^{-1}. Arrow B shows the same for 30 mg kg^{-1}.

calculated to be equivalent to therapeutic values of 30 mg kg^{-1} for methylprednisolone or 3 mg kg^{-1} for dexamethasone, for 1–3 days. None of these steroids is appreciably toxic to the cells but, on the other hand, exposure to 95% oxygen reduced growth rate to about 40% of control rate after 24 h, to about 20% of control after 48 h and to zero or to figures less than the starting counts after 72 h (Sturrock and Nunn, 1978).

From these results it may be concluded that these three steroids do not have any appreciable adverse effect on cell growth in concentrations which, in the case of methylprednisolone and dexamethasone, give useful protection against nuclear aberrations, but they do not protect cells against the depression of growth rate caused by oxygen.

DISCUSSION

High concentrations of oxygen are frequently required in clinical practice to maintain an adequate partial pressure of oxygen in the tissues. However, the therapeutic usefulness of such concentrations is limited by toxic manifestations in the lungs. The appearance of toxic effects is related to the species, the partial pressure of oxygen that actually reaches the cells and the duration of exposure. There is considerable variation in pulmonary sensitivity to oxygen, not only between different species of small animals and birds, but also between different strains, ages and sizes of animals within the same species. Neonatal and young animals were found to survive longer than adults when exposed to oxygen at high tensions (Clark and Lambertsen, 1971; Mustafa and Tierney, 1978; Yam, Frank and Roberts, 1978).

Mean survival times for all small adult mammalian species that have been tested were between 50 and 100 h of exposure to 90–100% oxygen. Monkeys were more resistant to oxygen lung damage and had average survival times longer than 400 h. Man is also more resistant than small animals and frogs were found to be highly resistant (Clark and Lambertsen, 1971).

There is not much variation between different experimental cell lines in their sensitivity to either oxygen at high concentrations or exposure to steroids. However, cultured lymphoma cells and lymphocytes from mouse, rat and rabbit were found to be sensitive to prednisolone, whereas those from guineapig, monkey and man were more resistant (Batra, Elrod and Schrek, 1966), and these results have been confirmed by Clamans, Moorhead and Benner, (1971), using hydrocortisone on thymus cells from man, guineapig and mouse.

Environmental oxygen concentrations greater than 30–40% were found to inhibit mitosis and DNA synthesis in both HeLa cells in culture (Reuckert and Mueller, 1960) and in mouse fibroblasts (Brosemer and Rutter, 1961). Allison (1965) working with HeLa cells, chick embryo cells and mouse macrophages showed that exposure of these cells to high concentrations of oxygen resulted in leakage of lysosomal enzymes into the surrounding media and this was reduced markedly by adding hydrocortisone or chloroquine to the culture media. However, Takala and Niinikoski (1974) suggested that the increased permeability of the cell walls was only secondary to the development of interstitial oedema. Northway, Petriceks and Shahinian (1972) exposed newborn mice to 96–100% oxygen and demonstrated a reduced uptake of tritiated thymidine which was associated with a partial inhibition of DNA synthesis.

The response of the adrenocortical system to hyperoxia at oxygen concentrations up to 101 kPa was not thought to be significant for at least 24 h of exposure, but at greater than atmospheric pressures the corticosterone content of the blood was increased in rats, after breathing oxygen at 303 kPa for 30 min and the adrenal glands were enlarged (Clark and Lambertsen, 1971). The extra corticosterone was thought to increase the rate of development of damage in the lungs. This has not been confirmed in germ-free animals (Mustafa and Tierney, 1978). On the other hand, hypophysectomy of rats before short exposures to oxygen at hyperbaric pressures of 585.8–717.1 kPa gave marked protection against pulmonary damage.

It has been suggested that steroids act by stabilizing the lipoproteins of cell membranes, including the membranes of lysosomes within the cells, thus preventing the release of hydrolase enzymes and disruption of the cells. Several workers have found that treatment with steroids *in vitro* has protected cells against some kinds of damage caused by exposure to high tensions of oxygen. Takala and Niinikoski (1974), who exposed rats to oxygen at 95–99% for various times, also gave daily injections of hydrocortisone to some animals which were exposed to oxygen for 60 h. They found that, although there was still pulmonary oedema in the steroid-treated rats, the lung beta-glucuronidase content was normal, whereas in rats not protected by steroid this enzyme had increased by about 100%. It was thought that this was a result of protection of lysosomal membranes by the hydrocortisone. Polet (1966) grew primary human amnion cells in medium containing cortisone for 30–60 days. He found that these cells were considerably protected against detachment and dispersion by trypsin and versene, substances usually employed to remove cells from the surface of vessels during cultural proceedings. The cells were also partly protected against solubilization by lauryl sulphate. It was considered that the steroid treatment had stabilized the cell membranes.

In our cell cultures we found that both methylprednisolone and dexamethasone could be used at a dose which reduced the frequency of nuclei damaged by oxygen to 50%, compared with 90% damage to cells not protected by steroids. The actual doses required are equivalent to 30–40 mg kg^{-1} of methylprednisolone or 4–5 mg kg^{-1} of dexamethasone for an average man and these figures correspond to the high dosage regimen recommended for treatment of septic shock (Schumer, 1976).

None of the three steroids in the doses at which we used them, when added to a cell culture in air, for up to 3 days, caused an appreciable reduction in growth rate of hamster cells, but they also had no protective effect on growth rate when the cells were grown in 95% oxygen. Therefore, there appear to be two distinct types of damage to the cells in this study, only one of which is benefitted by the use of steroids.

In clinical practice extremely high doses of prednisolone 30 mg kg^{-1}. have been recommended in the treatment of septic shock (Schumer, 1976) while the pulmonary disfunction associated with bypass surgery has been reduced by giving steroids (Replogle, Gazzaniga and Gross, 1966; Wilson, 1972). Gnanadurai and others (1978) have reduced the leakage of lysosomal enzymes during bypass surgery by the use of steroids. Furthermore, the injection of a single large dose of methylprednisolone, 30 mg kg^{-1}, was not found to be harmful to normal volunteers (Novak et al., 1970).

Although this paper reports positive results *in vitro* there is as yet, no evidence of any protective effect of steroids against the effects of oxygen in the intact animal or man.

REFERENCES

Allison, A. C. (1965). Role of lysosomes in oxygen toxicity. *Nature* (*Lond.*), **205**, 141.

Balin, A. K., Goodman, D. B. P., Rasmussen, H., and Cristofalo, V. J. (1976). The effect of oxygen tension on the growth and metabolism of WI-38 cells. *J. Cell. Physiol.*, **89**, 235.

Batra, K. V., Elrod, L. M., and Schrek, R. (1966). Species differences in the *in vitro* sensitivity of lymphocytes to prednisolone and x-rays. *J. Pharmacol. Exp. Ther.*, **152**, 525.

Brosemer, R. W., and Rutter, W. J. (1961). The effect of oxygen tension on the growth and metabolism of a mammalian cell. *Exp. Cell Res.*, **25**, 101.

Claman, H. N., Moorhead, J. M., and Benner, W. H. (1971). Corticosteroids and lymphoid cells *in vitro*. I. Hydrocortisone lysis of human, guineapig and mouse thymus cells. *J. Lab. Clin. Med.*, **78**, 499.

Clark, J. M., and Lambertsen, C. J. (1971). Pulmonary oxygen toxicity: a review. *Pharmacol. Rev.*, **23**, 37.

Conger, A. D., and Fairchild, L. M. (1952). Breakage of chromosomes by oxygen. *Proc. Natl Acad. Sci.* (*U.S.A.*), **38**, 289.

Gnanadurai, T. V., Branthwaite, M. A., Colbeck, J. F., and Welman, E. (1978). Lysosomal enzyme release from the lungs after cardiopulmonary bypass. *Anaesthesia*, **33**, 227.

Goetz, I. E. (1975). Oxygen toxicity in normal and neoplastic hamster cells in culture. *In Vitro*, **11**, 382.

Haugaard, N. (1965). Poisoning of cellular reactions by oxygen. *Ann. N.Y. Acad. Sci.*, **117**, 736.

—— (1968). Cellular mechanisms of oxygen toxicity. *Physiol. Rev.*, **48**, 311.

Kapanci, Y., Trosco, R., Eggermann, J., and Gould, V. E. (1972). Oxygen pneumonitis in man. *Chest*, **62**, 162.

Kaplan, H. P., Robinson, F. R., Kapanci, Y., and Weibel, E. R. (1969). Pathogenesis and reversibility of the pulmonary lesions of oxygen toxicity in monkeys. *Lab. Invest.*, **20**, 94.

Martindale (1977). *The Extra Pharmacopoeia*, 27th edn. (ed. A. Wade). London: The Pharmaceutical Press.

Mustafa, M. G., and Tierney, D. F. (1978). Biochemical and metabolic changes in the lung with oxygen, ozone, and nitrogen dioxide toxicity. *Am. Rev. Respir. Dis.*, **118**, 1061.

Northway, W. H., Petriceks, R., and Shahinian, L. (1972). Quantitative aspects of oxygen toxicity in the newborn: inhibition of lung DNA synthesis in the mouse. *Pediatrics*, **50**, 67.

Novak, E., Stubbs, S. S., Seckman, C. E., and Hearron, M. S. (1970). Effects of a single large intravenous dose of methylprednisolone sodium succinate. *Clin. Pharmacol. Ther.*, **11**, 711.

Pace, D. M., Thompson, J. R. and van Camp, W. A. (1962). Effects of oxygen on growth in several established cell lines. *J. Natl Cancer Inst.*, **28**, 897.

Polet, H. (1966). The effect of hydrocortisone on the membranes of primary human amnion cells *in vitro*. *Exp. Cell Res.*, **41**, 316.

Replogle, R. L., Gazzaniga, A. B., and Gross, R. E. (1966). Use of corticosteroids during cardiopulmonary bypass: possible lysosome stabilization. *Circulation*, **33** and **34** (Suppl. 1), 86.

Rueckert, R. R., and Mueller, G. C. (1960). Effect of oxygen tension on HeLa cell growth. *Cancer Res.*, **20**, 944.

Schumer, W. (1976). Steroids in the treatment of clinical septic shock. *Ann. Surg.*, **184**, 333.

Smith, J. L. (1899). The pathological effects due to increase of oxygen tension in the air breathed. *J. Physiol. (Lond.)*, **24**, 19.

Sturrock, J. E., and Nunn, J. F. (1978). Chromosomal damage and mutations after exposure of Chinese hamster cells to high concentrations of oxygen. *Mutation Res.*, **57**, 27.

Swartz, H. M. (1973). Toxic oxygen effects. *Int. Rev. Cytol.*, **35**, 321.

Takala, I., and Niinikoski, J. (1974). Role of lysosomal damage in the development of pulmonary oxygen poisoning. *Acta Chir. Scand.*, **140**, 167.

Weibel, E. R., (1971). Oxygen effect on lung cells. *Arch. Intern. Med.*, **128**, 54.

Weissmann, G. (1964). Labilization and stabilization of lysosomes. *Fed. Proc.*, **23**, 1038.

Wilson, J. W. (1972). Treatment or prevention of pulmonary cellular damage with pharmacologic doses of corticosteroid. *Surg. Gynecol. Obstet.*, **134**, 675.

Yam, J., Frank, L., and Roberts, R. J. (1978). Oxygen toxicity: comparison of lung biochemical response in neonatal and adult rats. *Pediatr. Res.*, **12**, 115.

EFFET PROTECTEUR DES STEROIDES SUR LES CULTURES DE CELLULES ENDOMMAGEES PAR DE FORTES CONCENTRATIONS D'OXYGENE

RESUME

Les anomalies des chromosomes résultant de l'exposition des cellules fibroblastes de poumon de hampster chinois à 95% d'oxygène ont été utilisées pour faire des recherches sur l'effet protecteur de trois stéroides. L'hydrocortisone n'a eu que peu d'effet utile. Les doses de méthylprednisolone et de déxaméthasone ont, cependant, pu être augmentées jusqu'à un niveau permettant de diminuer de 50% les dégâts causés aux noyaux par l'oxygène, contre 90% de dégâts causés aux cellules non protégées par les stéroïdes. Il n'y a eu aucune altération de la croissance des cellules. Les concentrations de stéroïdes requises pour obtenir cet effet ont respectivement été de 100 et de 10 μmol litre^{-1}, ce qui correspond à la plus forte dose actuellement utilisée pour protéger les poumons contre les effets des chocs endotoxiques, des hémorragies et autres. Les stéroïdes n'ont donné aucune protection contre la dépression de la croissance des cellules causée par les 95% d'oxygène.

DIE SCHUTZWIRKUNG VON STEROIDEN AUF KULTIVIERTE, DURCH HOHE SAUERSTOFF-KONZENTRATIONEN BESCHÄDIGTE ZELLEN

ZUSAMMENFASSUNG

Chromosomaberrationen, die infolge vom Aussetzen der Lungenfibroblastzellen des chinesischen Hamsters an 95%-igem Sauerstoff hervorgerufen wurden, sind zum Studium der Schutzwirkung von drei Steroiden eingesetzt worden. Die nützliche Wirkung von Hydrocortisone war gering, dagegen konnte Dosierung sowohl mit Methylprednisolone als auch mit Dexamethasone auf eine Stufe gesteigert werden, wo die Beschädigung durch Sauerstoff auf 50% der Zellkerne reduziert wurde, verglichen mit 90% bei Zellen, die nicht durch Steroiden geschützt wurden. Das Zellenwachstum wurde dabei nicht bedeutend beeinträchtigt. Die Konzentrationen von Steroiden, die dazu benötigt wurden, waren 100 bzw. 10 μmol litre^{-1}, was dem hohen Dosierungsplan entspricht, der zur Zeit zum Schutz der Lungen gegen die Auswirkungen von Endotoxinschock, Blutung und andere Zustände verordnet wird. Die Steroiden stellten jedoch keinen Schutz gegen die Herabsetzung des Zellenwachstums dar, die durch 95%-igen Sauerstoff hervorgerufen wurde.

EFECTOS PROTECTORES DE LOS ESTEROIDES SOBRE CELULAS CULTIVADAS DAÑADAS POR ALTAS CONCENTRACIONES DE OXIGENO

SUMARIO

Se usó las aberraciones cromosomales resultantes de la exposición de células fibroblásticas del pulmón de ratas chinas al oxígeno al 95% para averiguar el efecto protector de tres esteroides. La hidrocortisona tuvo un efecto poco útil. Sin embargo, puede incrementarse la dosificación tanto de la metilprednisolona como de la dexametasona hasta un nivel en el cual el daño por el oxígeno se reduce en un 50% de los núcleos en comparación con un daño del 90% en células noprotegidas por esteroides. No hubo ningún impedimento substancial del crecimiento de las células. Las concentraciones de esteroides necesarias para este efecto fueron de 100 y 10 μmol litre^{-1}, respectivamente, lo que corresponde a un regimen de alta dosificación utilizado en la actualidad para proteger los pulmones contra los efectos del choque endotóxico, de las hemorragias y de otras condiciones. Los esteroides no protegieron contra la depresión del crecimiento celular ocasionada por el oxígeno al 95%.

Br. J. Anaesth. (1980), **52**, 573

HALOTHANE ANAESTHESIA CAN BLOCK INSULIN STIMULATION OF PYRUVATE DEHYDROGENASE ACTIVITY IN MAMMARY GLANDS OF 24-HOUR STARVED LACTATING RATS

C. E. HUTCHINSON AND H. G. COORE

SUMMARY

The effect of halothane anaesthesia on the activity of the mitochondrial enzyme pyruvate dehydrogenase was studied in starved lactating rats. Extracts of freeze-clamped mammary gland and liver were assayed for pyruvate dehydrogenase activity. The fraction of the enzyme in the phosphorylated inactive form was increased greatly by starvation or by streptozotocin diabetes, and halothane anaesthesia did not distrub this effect. In starved animals not exposed to halothane, injection of insulin led to a rapid increase in the active fraction of the enzyme in mammary gland but not in liver. In animals under halothane anaesthesia this effect of insulin was largely abolished. The combination of starvation and halothane anaesthesia may impair mitochondrial accumulation of calcium which may be involved in the stimulation of pyruvate dehydrogenase by insulin.

Since the studies of the effects of volatile anaesthetics on enzymes should be relevant to clinical usage (Taussig, 1979), the use of anaesthesia adequate for surgery and the selection of enzymes whose activities in the tissues can be directly studied or inferred are essential.

The mammalian multi-enzyme complex pyruvate dehydrogenase (PDH) is purely mitochondrial in location and is regulated by phosphorylation (inactivation) and dephosphorylation (activation) (Linn et al., 1969). The reaction catalysed by the enzyme is

$$\begin{aligned}&CH_3.CO.COOH + NAD + CoA\\&\qquad\longrightarrow CH_3.CO.CoA + NADH + CO_2\end{aligned}$$

This reaction is effectively unidirectional and this fact and the relatively low activity of PDH in most tissues suggest that the enzyme complex is the major regulatory site controlling the rate of pyruvate oxidation or incorporation of pyruvate carbon into fatty acids, or both. *In-vitro* studies with purified enzyme or with isolated mitochondria have shown that the products of the reaction, NADH and acetyl CoA, inhibit the reaction directly and by stimulating the kinase which phosphorylates the enzyme. Furthermore, there is good evidence that, under certain conditions *in-vitro* a small intra-mitochondrial ratio [ATP]/[ADP] favours dephosphorylation and activation of the enzyme complex and small intra-mitochondrial concentrations of magnesium and calcium ions favour phosphorylation and inactivation of the enzyme complex (Denton et al., 1975). It is more difficult to assign relative importance to these individual factors in controlling PDH in tissue *in situ*. However, by freeze-clamping tissue *in situ* and by appropriate extraction of the tissue, it is possible to determine the total activity of the enzyme complex after complete dephosphorylation *in vitro* (PDH_T activity) and also the portion of the enzyme activity which existed in this dephosphorylated form *in vivo* before extraction (PDH_a activity). This technique has been applied successfully to lactating mammary gland, muscle, adipose tissue, kidney, heart and liver of rats (Wieland et al., 1971; Wieland, Patzelt and Löffler, 1972; Hennig, Löffler and Wieland, 1975; Field and Coore, 1976; Stansbie et al., 1976).

The effects of halothane (2-bromo-2-chloro-1,1,1,-trifluorethane) anaesthesia on the phosphorylation status of PDH could indicate likely effects of the anaesthetic on pyruvate disposal which has implications for ATP generation and lipogenesis. Furthermore, since changes in the phosphorylation status of PDH can reflect alterations of intra-mitochondrial free magnesium and calcium ions and ratios of [NADH]/[NAD], [Acetyl CoA]/[CoA] and [ATP]/[ADP] (Denton et al., 1975), the effects of halothane in promoting or inhibiting such changes in the phosphorylation status of PDH can be a useful index of the impact of the anaesthetic on mitochondrial function. In this laboratory it has been found that

---

CHARLES E. HUTCHINSON, B.SC., Biochemistry Department, Birmingham University, P.O. Box 363, Birmingham B15 2TT. HALDANE G. COORE, M.B., CH.B., PH.D., Biochemistry Department, University of the West Indies, Kingston, Jamaica.

0007-0912/80/060573-04 $01.00

© Macmillan Journals Ltd 1980

24-h starvation increased the phosphorylated inactive fraction of PDH in lactating rat mammary gland and that a large dose of insulin rapidly reversed this effect of starvation (Baxter and Coore, 1978). We have used this response to insulin as a test system to examine the effects of halothane anaesthesia. We considered that 24-h starvation was an appropriate condition since it approximates to the clinical situation when halothane is used. We have found that, although PDH activity in mammary gland or liver of starved lactating rats was undisturbed by halothane, there was a severe inhibition of the response to insulin of the enzyme in mammary gland.

METHODS

Rats, materials and methods were generally as described earlier (Field and Coore, 1976).

Since anaesthesia was required for freeze-clamping, the experiments were designed to compare effects of minimal exposure to the anaesthetic (just sufficient to permit freeze clamping) with prolonged exposure, 30-60 min, including the time of injection and the interval before freeze clamping.

Injections were given when animals were under either halothane or very light ether anaesthesia. The induction of halothane anaesthesia was performed by placing the rat in a dessicator jar through which passed a stream of halothane 7% in oxygen 1 litre min^{-1}. After induction of anaesthesia the rat was placed on a dissecting board with its head enclosed in a small plastic funnel through which passed halothane 4–5% in oxygen 0.5 litre min^{-1}. Dissection commenced when the animal showed no reflex response to pinching of the skin with forceps. Less than 5 min was required to expose a suitable portion of mammary gland or liver and to clamp it in aluminium tongs cooled in liquid nitrogen. The frozen tissue was powdered under liquid nitrogen and kept in a glass bottle on solid carbon dioxide until the time of extraction, which was less than 1 h. Weighed portions of the powder (200–400 mg) were extracted with a motor-driven Teflon-in-glass homogenizer into 2 ml of either ice-cold triethanolamine buffer 25 mmol litre^{-1}, pH 7, EDTA 5 mmol litre^{-1} and mercaptoethanol 7 mmol litre^{-1} or ice-cold triethanolamine buffer 30 mmol litre^{-1}, pH 7 and mercaptoethanol 7 mmol litre^{-1}. Assay of PDH in the former medium by the method of Coore and others (1971) yielded data for activity of the initially dephosphorylated enzyme (PDH_a activity). The presence of EDTA in this medium prevented activities of the accessory enzymes which phosphorylate and dephosphorylate PDH. To the second extract was added excess magnesium, calcium and the dephosphorylating enzyme and the mixture was incubated at 30 °C for 10 min. Assay of PDH activity after this incubation gave values of total enzyme activity (PDH_T activity). The ratio of $\text{PDH}_a/\text{PDH}_T$ activities multiplied by 100 is referred to as percentage PDH_T activity. Further details of experimental design are given in the legend to table I.

RESULTS

Both 24-h starvation and streptozotocin diabetes (tables I and II) reduce percentage PDH_T activity in mammary gland extracts below the 40% value found in normal fed animals (Baxter and Coore, 1978). Table I shows that 30 min of exposure to halothane did not disturb the percentage of active enzyme or the total activity of PDH in liver or mammary glands of starved animals. In other experiments (data not given) we have found also that [ATP]/[ADP] in these gland extracts was the same after 30 min as after 5 min of exposure of the animals to halothane. However, the effect of a large dose of insulin in promoting *in vivo* dephosphorylation of PDH in mammary gland was largely inhibited during 30 min of halothane. The hypoglycaemic effect of the hormone was undisturbed. This made it unlikely that halothane interfered with any early event in hormone action, for example, the hormone–receptor interaction. Confirmation of this conclusion is found in table II where it is seen that the injection of insulin in the presence or absence of halothane anaesthesia was able to correct the effect of streptozotocin diabetes on percentage PDH_T activity in mammary gland. The hypoglycaemic effect of insulin 60 min after injection was, if anything, greater when the animals were maintained under halothane than when not anaesthetized continuously.

DISCUSSION

Starvation diminishes circulating insulin in lactating rats (Robinson, Gerard and Williamson, 1978). There is no information regarding effects of starvation on insulin receptors in the mammary gland, but in adipose tissue there is no decrease in the number of such receptors and their affinity for insulin is increased (Olefsky, 1976; Kasuga et al., 1977). Streptozotocin diabetes is associated with concentrations of circulating insulin which are probably less than is the case in starvation (Robinson, Gerard and Williamson, 1978), but the effect of streptozotocin diabetes on mammary gland PDH was evidently correctable by the administration of insulin irrespective of the

TABLE I. *Effects of insulin injection and halothane anaesthesia on PDH activity in mammary glands and livers of 24-h starved lactating rats. Experiments yielding data of top two rows involved injection of animals which had been very lightly anaesthetized with ether. Immediately after injection the rats recovered consciousness and remained undisturbed for 25 min. They were then placed under halothane anaesthesia and the appropriate tissues exposed and freeze-clamped. Blood was obtained from the severed jugular veins. In the experiments yielding data of bottom two rows animals were placed under halothane anaesthesia, injected and maintained under the anaesthetic until the time of freeze-clamping. The times refer to the intervals between injections and freeze-clamping. PDH_T activity is expressed for gram wet weight. iu = international unit of soluble insulin which was injected i.p.* $^{**}P < 0.01$, $^{***}P < 0.001$ v. *data in top row;* † $P < 0.001$ *for difference of row four and row two according to Student's t test.* (*Number of rats in parentheses*)

Treatment of rats	Percentage PDH_T activity in mammary gland extracts	PDH_T activity in mammary gland extracts (unit g^{-1})	Percentage PDH_T activity in liver extracts	PDH_T activity in liver extracts (unit g^{-1})	Plasma glucose at time of freeze-clamping (mmol litre^{-1})
Saline injected 30 min before, minimal halothane	10.5 ± 0.9 (6)	1.55 ± 0.21 (6)	6.1 ± 0.6 (4)	1.68 ± 0.19 (4)	7.9 ± 0.5 (6)
Insulin 10 iu injected 30 min before minimal halothane	23.5 ± 1.2*** (6)	1.61 ± 0.16 (6)	6.1 ± 0.1 (4)	1.68 ± 0.12 (4)	1.8 ± 0.1*** (6)
Halothane anaesthesia, saline injected 30 min before freeze-clamping	10.4 ± 0.2 (6)	1.75 ± 0.82 (6)	7.6 ± 2.3 (4)	1.10 ± 0.28 (4)	7.3 ± 0.4 (6)
Halothane anaesthesia, insulin 10 iu injected 30 min before freeze-clamping	13.8 ± 0.9**† (6)	1.47 ± 0.60 (6)	5.8 ± 0.5 (4)	1.63 ± 0.11 (3)	1.4 ± 0.5*** (6)

TABLE II. *Effects of insulin injection and halothane anaesthesia on PDH activity in mammary glands of streptozotocin-diabetic lactating rats. Rats were injected i.p. with streptozotocin* 16 *mg in* 0.3 *ml of sodium acetate* 10 *mmol litre*$^{-1}$, *pH* 4.5, 2 *h before other injections. For further explanation of treatments, enzyme units and significance tests see legend to table I.*

Treatment of rats	Percentage PDH_T activity in mammary gland extracts	PDH_T activity in mammary gland extracts (unit g^{-1})	Plasma glucose at time of freeze-clamping (mmol litre^{-1})
Saline injected 60 min before, minimal halothane	5.7 ± 1.1 (5)	1.56 ± 0.04 (5)	18.4 ± 2.6 (8)
Insulin 10 iu injected 60 min before, minimal halothane	33.5 ± 2.1*** (4)	1.56 ± 0.04 (4)	3.5 ± 0.4*** (4)
Halothane anaesthesia, saline injected 60 min before freeze-clamping	8.3 ± 2.2 (4)	1.48 ± 0.05 (4)	19.4 ± 2.1 (4)
Halothane anaesthesia, insulin 10 iu injected 60 min before freeze-clamping	30.8 ± 6.8*** (5)	1.56 ± 0.11 (5)	1.32 ± 0.17***† (5)

presence of halothane. It appears that starvation caused changes in the metabolism of mammary tissue which were reinforced by halothane such that insulin could less easily set in train the events which lead to dephosphorylation of PDH. The absence of effect of the anaesthetic itself on PDH agrees with an earlier report of *in vitro* experiments (Bennett et al., 1978). It is likely that the combination of halothane anaesthesia and starvation interferes with some aspect of mitochondrial function which is necessary for insulin action on PDH. One possibility is mitochondrial accumulation of calcium ions which may be inhibited by halothane (Rosenberg and Haugard, 1973). It has been suggested (Denton et al., 1975) that insulin action on adipose tissue PDH involves an increase in mitochondrial free calcium ions.

ACKNOWLEDGEMENT

We are grateful to the Medical Faculty, University of Birmingham, for financial assistance in the purchase of animals and materials.

REFERENCES

Baxter, M. A., and Coore, H. G. (1978). The mode of regulation of pyruvate dehydrogenase of lactating rat mammary gland. *Biochem. J.*, **174**, 553.

Bennett, D., Cain, P., Ellis, F. R., Halsall, J., and Louis C. F. (1978). Effect of halothane on the rate of acid production, lactate production and pyruvate dehydrogenase activity in malignant hyperpyrexia human muscle. *Br. J. Anaesth.*, **50**, 799.

Coore, H. G., Denton, R. M., Martin, B. R., and Randle, P. J. (1971). Regulation of adipose tissue pyruvate dehydrogenase by insulin and other hormones. *Biochem. J.*, **125**, 115.

Denton, R. M., Randle, P. J., Bridges, B. J., Cooper, R. H., Kerbey, A. C., Pask, H. T., Severson, D. L., Stansbie, D., and Whitehouse, S. (1975). Regulation of mammalian pyruvate dehydrogenase. *Molec. Cell. Biochem.*, **9**, 27.

Field, B., and Coore, H. G. (1976). Control of rat mammary gland pyruvate dehydrogenase by insulin and prolactin. *Biochem. J.*, **156**, 333.

Hennig, G., Löffler, G., and Wieland, O. H. (1975). Active and inactive forms of pyruvate dehydrogenase in skeletal muscle as related to the metabolic and functional state of the muscle cell. *FEBS Lett.*, **59**, 142.

Kasuga, M., Akanuma, Y., Iwamoto, Y., and Kosaka, K. (1977). Effects of fasting and refeeding on insulin receptors and glucose metabolism in rat adipocytes. *Endocrinology*, **100**, 1384.

Linn, T. C., Pettit, F. H., Hucho, F., and Reed, L. J. (1969). α Keto-acid regulatory complexes. XI: Comparative studies of regulatory properties of the pyruvate dehydrogenase complexes from kidney heart and liver mitochondria. *Proc. Natl Acad. Sci. U.S.A.*, **64**, 227.

Olefsky, J. M. (1976). Effects of fasting on insulin binding, glucose transport and glucose oxidation in isolated rat adipocytes, *J. Clin. Invest.*, **58**, 1450.

Robinson, A. M., Gerard, J. R., and Williamson, D. H. (1978). Evidence for a role of insulin in the regulation of lipogenesis in lactating rat mammary gland. *Biochem. J.*, **176**, 343.

Rosenberg, H., and Haugard, N. (1973). The effect of halothane on metabolism and calcium uptake in mitochondria of the rat liver and brain. *Anesthesiology*, **39**, 44.

Stansbie, D., Denton, R. M., Bridges, B. J., Pask, H. T., and Randle, P. J. (1976). Regulation of pyruvate dehydrogenase and pyruvate dehydrogenase phosphatase activity in rat epididymal fat pads. *Biochem. J.*, **154**, 225.

Taussig, P. E. (1979). Biochemical mechanisms in anaesthesia. *Int. J. Biochem.*, **10**, 183.

Wieland, O. H., Patzelt, C. and Löffler, G. (1972). Active and inactive forms of pyruvate dehydrogenase in rat liver. *Eur. J. Biochem.*, **26**, 426.

—— Siess, E., Schulze-Wethmar, F. H., v. Funcke, H. G., and Winton, B. (1971). Active and inactive forms of pyruvate dehydrogenase in rat heart and kidney; effect of diabetes, fasting and refeeding on pyruvate dehydrogenase interconversion. *Arch. Biochem. Biophys.*, **143**, 593.

L'ANESTHESIE A L'HALOTHANE PEUT BLOQUER LA STIMULATION PAR L'INSULINE DE L'ACTIVITE DU PYRUVATE DESHYDROGENASE DANS LES GLANDES MAMMAIRES DE RATES ALLAITANTES PRIVEES DE NOURRITURE PENDANT 24 HEURES

RESUME

On a étudié sur des rates allaitantes et affamées l'effet de l'anesthésie à l'halothane sur l'activité de l'enzyme mitochondrial pyruvate déshydrogénase. Des extraits de glandes mammaires et de foie congelés ont été soumis à des essais pour déterminer l'activité pyruvate déshydrogénase. La fraction de l'enzyme sous la forme inactive phosphorylée a été grandement accrue par le jeûne ou par le diabète streptozotocine, et l'anesthésie à l'halothane n'a pas perturbé cet effet. Chez les animaux affamés non exposés à l'halothane, une injection d'insuline a entraîné une augmentation rapide de la fraction active de l'enzyme dans la glande mammaire, mais pas dans le foie. Chez les animaux soumis à une anesthésie à l'halothane cet effet de l'insuline a été fortement amoindri. La combinaison du jeûne et de l'anesthésie à l'halothane peut altérer l'accumulation mitochondriale de calcium, qui peut être mis en cause dans la stimulation de pyruvate déshydrogénase par l'insuline.

HALOTHAN-ANÄSTHESIE KANN INSULIN-STIMULIERUNG DER PYRUVATDEHYDROGENASE-AKTIVITÄT IN DEN BRUSTDRÜSEN AUSGEHUNGERTER, SÄUGENDER RATTEN BLOCKIEREN

ZUSAMMENFASSUNG

Der Effekt einer Halothannarkose auf die Aktivität der mitochondrialen Enzym-Pyruvat-Dehydrogenase wurden bei ausgehungerten, säugenden Ratten studiert. Extrakte der Brustdrüse und Leber wurden auf Pyruvat-Dehydrogenaseaktivität getestet. Der Gehalt des Enzyms in seiner phosphorylierten, inaktiven Form wurde durch Aushungerung oder Streptozotocyn-Diabetes stark erhöht, was durch Halothannarkose nicht beeinträchtigt wurde. Bei ausgehungerten Tieren ohne Halothan führte eine Insulininjektion zu aktivem Ansteigen des aktiven Gehalts des Enzymes in der Brustdrüse, aber nicht in der Leber. Bei Tieren unter Halothannarkose war diese Insulinwirkung weitgehend eliminiert. Die Kombination von Aushungerung und Halothannarkose könnte die mitochondriale Akkumulierung von Kalzium beeinträchtigt werden, die an der Stimulierung der Pyruvat-Dehydrogenase durch Insulin beteiligt sein könnte.

LA ANESTESIA POR HALOTANO PUEDE BLOQUEAR LA ESTIMULACION POR INSULINA DE LA ACTIVIDAD DE LA DESHIDROGENASA DEL PIRUVATO EN LAS GLANDULAS MAMARIAS DE RATONES LACTANTES HAMBREADOS DURANTE 24 HORAS

SUMARIO

Se hizo un estudio en ratones lactantes del efecto de la anestesia por halotano sobre la actividad de la deshidrogenasa de piruvato de la enzima mitocondrial. Se hicieron pruebas con extractos de hígado y glándulas mamarias sometidos a congelación respecto de la actividad de deshidrogenasa de piruvato. La fracción de la enzima en la forma inactiva fosforilatada aumentó considerablemente por el hambre o por la diabetes de estreptozotocina y la anestesia por halotano no alteró este efecto. En los animales hambrientes no-expuestos al halotano, la inyección de insulina produjo un aumento rápido de la fracción activa de la enzima en la glándula mamaria pero no en el hígado. En los animales sometidos a la anestesia por halotano, este efecto de la insulina fue eliminado mayormente. La combinación del hambre y de la anestesia por halotano no impidió la acumulación mitocondrial del calcio que puede tener alguna influencia en la estimulación de la deshidrogenasa del piruvato por la insulina.

Br. J. Anaesth. (1980), **52**, 577

HALOTHANE IMPROVES THE BALANCE OF OXYGEN SUPPLY TO DEMAND IN ACUTE EXPERIMENTAL MYOCARDIAL ISCHAEMIA

G. Smith, K. Rogers and J. Thorburn

SUMMARY

Acute myocardial infarction was induced by ligation of the anterior descending branch of the left main coronary artery in greyhound dogs anaesthetized with pentobarbitone. Blood flow in the area of ischaemia was measured by xenon clearance and compared with flow in the circumflex artery measured with electromagnetic flow meters. Halothane 1% produced an approximate 40% reduction in flow to both ischaemic and normal areas in association with a 20% reduction in collateral perfusion pressure and a 40% reduction in mean arterial pressure. Comparison of the percentage change in the ratio of oxygen availability/consumption in response to halothane revealed a significant difference between the ischaemic and the normal areas. The former increased to 113 ± 9.3% (mean ± SEM) whilst the latter decreased to 91 ± 5.02%. This suggests that, in the non-failing heart, halothane improves oxygenation in areas of acute myocardial ischaemia.

It is well known that halothane produces a dose-related depression of myocardial function accompanied by decreases in myocardial oxygen consumption and coronary blood flow (Smith et al., 1974; Merin, Kumazawa and Luka, 1976; Merin, Verdouw and de Jong, 1977). Although the major factor contributing to the decrease in coronary blood flow is the negative inotropic action of halothane, it has been suggested that, in addition, halothane may have direct effects on the coronary vessels, producing either vasoconstriction (Smith et al., 1974; Vance et al., 1975; Vance et al., 1979) or vasodilatation (Vatner and Smith, 1974; Domenech et al., 1977). Such effects may be important during anaesthesia for patients with coronary artery disease and impaired perfusion of the myocardium, since vasodilatation may produce "coronary stealing" and be associated with diminution in perfusion of an ischaemic area of myocardium (Fam and McGregor, 1964). In contrast, theoretically, vasoconstriction may be beneficial by maintaining perfusion of an ischaemic area.

One approach to this problem has been to study the effect of halothane on the epicardial e.c.g. in experimental canine myocardial ischaemia (Bland and Lowenstein, 1976). Halothane produced an improvement in the e.c.g. pattern and it was postulated that it improved the ratio of oxygen supply to demand in the ischaemic area.

We have measured both oxygen consumption and oxygen supply in an ischaemic area of the canine myocardium to assess alterations in the response to halothane and compared these with events occurring in normal myocardium.

METHODS

Anaesthesia was induced in 15 greyhounds with pentobarbitone 30 mg kg^{-1} and endotracheal intubation performed following the administration of suxamethonium 100 mg i.v. The lungs were ventilated with a mixture of oxygen and nitrogen at a tidal volume of 10–12 ml kg^{-1} adjusted to produce Pa_{CO_2} approximately 5.3 kPa. The inspired gas concentrations were adjusted to produce Pa_{O_2} approximately 12.7–13.3 kPa.

Catheters were inserted via the femoral vessels into the descending aorta and inferior vena cava under radiographic control. A Sones catheter was inserted into the left ventricle via the common carotid artery and a second catheter was inserted via the jugular vein to the coronary sinus, as described previously (Smith et al., 1974). A Swan–Ganz catheter was inserted via the external jugular vein to the pulmonary artery for measurement of cardiac output by the thermal dilution technique (Devices).

Following left thoracotomy via the 5th interspace, the heart was exposed, the pericardium incised and a short section (2–3 mm) of the circumflex branch of the left main coronary artery dissected out. Around

---

G. Smith,* B.Sc., M.D., F.F.A.R.C.S.; K. Rogers, F.F.A.R.C.S.; J. Thorburn, F.F.A.R.C.S.; University Department of Anaesthesia and Division of Anaesthesia, Western Infirmary, Glasgow.

* Present address, for correspondence: University Department of Anaesthesia, The General Hospital, Gwendolen Road, Leicester.

0007–0912/80/060577–07 $01.00

© Macmillan Journals Ltd 1980

this was placed an appropriate (2 or 2.5-mm) electromagnetic flow transducer (Statham SP7515) connected to a flowmeter (Statham SP2202) with non-occlusive zero facility. The correlation coefficient for flow measured in this manner against flow measured by collection into a graduated cylinder is 0.99. This flow was regarded as that to essentially normal myocardium and blood from the coronary sinus was regarded as venous drainage from essentially normal myocardium.

At a point approximately two-thirds distant from the apex to the base of the heart a short segment of the anterior descending branch of the left main coronary artery was dissected and occluded by tying. The artery was catheterized distally with a fine nylon catheter. The pressure produced in the occluded vessel by the collateral circulation was measured using an Elema-Schönander (EMT35) transducer (distal perfusion pressure or DPP). Myocardial blood flow in the ischaemic area supplied by the occluded vessel was measured by the injection of a small quantity (0.1–0.2 ml) of radioactive xenon-133 dissolved in saline and the external counting of the washout of xenon-133 using a highly collimated scintillation counter. This technique is based on the principle described by Ross and colleagues (1964) and its use in our laboratory for measurement of normal myocardial flow was described by Ledingham and co-workers (1970) and for the ischaemic myocardium by Marshall, Parratt and Ledingham (1974).

A collateral vein adjacent to the occluded artery was cannulated using a 10-cm Teflon cannula (Longdwell). Blood was sampled from this vein for measurement of gas tensions; this was regarded as blood drainage essentially from the ischaemic area of myocardium. Approximately 1 h was allowed to elapse following coronary arterial occlusion, and during this time seven of the 15 dogs died. Thus the study was completed on only eight dogs (greyhounds weight 24–28 kg).

Following duplicate sets of control measurements halothane 1.0% was introduced into the inspired gas and further sets of measurements obtained 5, 15 and 30 min later. The halothane was discontinued and a further set of data obtained 15 min later.

Blood samples (1 ml) were withdrawn anaerobically from the descending aorta, coronary sinus, pulmonary artery and coronary vein. P_{O_2}, P_{CO_2} and pH of these samples were measured using appropriately calibrated electrodes (Instrumentation Laboratories IL 213). Oxygen, carbon dioxide and pH values were corrected for any temperature difference between the electrodes and the mid-oesophageal temperature of the animal (measured with a thermocouple (Ellab)). The accuracy of the IL P_{O_2} electrode in the range 2.6–6.5 kPa was assessed as follows: Gas mixtures were prepared using the IL 208 gas mixing module which allows mixing of two cylinders in any proportion. Two cylinders were chosen—5.6% carbon dioxide in air and 5.6% carbon dioxide in nitrogen. Part of the output of the mixer was fed to the electrode and part to the Servomex analyser (Servomex OA 101 Mk II, which has an accuracy of 0.1% oxygen). Both electrode and Servomex were calibrated using the same cylinder as supplied by the gas mixer. For the air setting the Servomex was set to the specified percentage of the cylinder (20.7%) and the P_{O_2} derived from the dry barometric pressure. Nine calibrations were obtained on one day and 15 points on a second day for the range 3.72–6.37. The following regression was obtained:

$$P_{O_2}\,(\text{IL}) = 0.97\,(P_{O_2}\text{-Servomex}) + 0.11 \quad (r = 0.996)$$

Haemoglobin was measured using a Co-oximeter (Instrumentation Laboratories Inc.) and blood oxygen content calculated using the equation:

$$\text{Hb}(\text{g dl}^{-1}) \times 1.39 \times \%\text{satn} + P_{O_2}(\text{kPa}) \times 0.023$$

There is a good correlation between this method of calculation of oxygen content and that by the method of Van Slyke (Ledingham et al., 1970).

Derived data were obtained as follows:

Normal myocardial oxygen consumption (ml min^{-1}) = mean coronary flow (ml min^{-1}) × (arterial oxygen − coronary sinus oxygen content) (ml dl^{-1}).

Normal myocardial oxygen availability (ml min^{-1}) = mean coronary flow (ml min^{-1}) × arterial oxygen content (ml dl^{-1}).

Oxygen extraction (%) = (arterial oxygen content − coronary sinus oxygen content)/(arterial oxygen content).

Diastolic coronary resistance (unit) = (systemic diastolic pressure − LVEDP)/(diastolic coronary flow).

Mean coronary artery resistance (unit) = (mean systemic arterial pressure)/(mean coronary flow).

Ischaemic area oxygen consumption (ml min^{-1} per 100 g) = infarct flow (ml min^{-1} per 100 g) × (arterial − coronary vein) oxygen content (ml dl^{-1}).

Ischaemic area oxygen availability (ml min^{-1} per 100 g) = infarct flow (ml min^{-1} per 100 g) × (arterial oxygen content) (ml dl^{-1}).

Infarct vessel resistance (unit) = 100 × (mean DPP − LVEDP)/(infarct flow).

Infarct oxygen extraction (%) = (arterial − coronary vein) oxygen content/(arterial oxygen content).

Infarct flow resistance (unit) = 100 (mean distal perfusion pressure − LVEDP)/(infarct flow).

Data shown in tables I–III were analysed by paired Student's *t* test and those in figures 1–4 by unpaired Student's *t* test.

All calculations were performed on an appropriately programmed Hewlett-Packard desk-top computer (9815A/S).

RESULTS

The introduction of halothane 1.0% to the inspired gases was associated with decreases in cardiac output (CO), mean arterial pressure (m.a.p.) and heart rate (HR), all of which were significant by 30 min. Fifteen minutes after discontinuing halothane there were significant increases in HR, m.a.p. and CO in comparison with the values at 30 min of halothane administration (table I). Although heart rate was restored to the value present before the administration of halothane, cardiac output and arterial pressure had not returned to control values at the time of the final measurements (table I). There were no significant changes in left ventricular end-diastolic pressure.

For the normal area of myocardium, there was a significant decrease in coronary blood flow by 15 min after introduction of halothane and further significant reductions at 30 min (table II). The mean flow decreased to 44% of the control value after 30 min, but was restored to only 66% of the control value 15 min after discontinuing halothane; this was significantly less than the control. Similar changes occurred in diastolic coronary flow, but there were no significant changes in either mean or diastolic coronary artery resistance. Changes in myocardial oxygen consumption were similar to those in myocardial flow and myocardial oxygen availability, there being significant decreases in response to halothane followed by an increase on discontinuing the drug. Although myocardial oxygen extraction increased in response to halothane this was not significant, but there was a significant decrease 15 min after discontinuing halothane in comparison with the 30-min measurement (table II).

TABLE I. *Haemodynamic data before and after administration of halothane* (1% *inspired concentration*) *to dogs with acute myocardial ischaemia* (*mean* ± *SEM*; n = 8). **Indicates* $P < 0.05$ *in comparison with control.* † $P < 0.05$ *in comparison with 30-min data*

		Halothane			After halothane
	Control	5 min	15 min	30 min	15 min
Heart rate (beat min^{-1})	158 ± 6.2	152 ± 4.5	139 ± 9.0	135 ± 9.0*	154 ± 10†
Mean arterial pressure (mm Hg)	124 ± 4.0	99 ± 5.0	79 ± 8.0*	72 ± 7.0*	98 ± 5.0†
LVEDP (mm Hg)	7.5 ± 1.1	8 ± 1.4	8.7 ± 2.2	6.7 ± 1.5	6.5 ± 1.7
Cardiac output (litre min^{-1})	4.6 ± 0.5	3.6 ± 0.5	3.2 ± 0.5	3.1 ± 0.4*	3.5 ± 0.4

TABLE II. *Data relating to normal area of myocardium in dogs with acute myocardial ischaemia, before and after administration of halothane* (1% *inspired concentration*) (*mean* ± *SEM*; n = 8). $P < 0.05$ *in comparison with control.* † $P < 0.05$ *in comparison with 30-min data*

		Halothane			After halothane
	Control	5 min	15 min	30 min	15 min
Mean flow (ml min^{-1})	45.6 ± 4.8	28.3 ± 1.7	22.2 ± 2.2*	20.1 ± 1.2*	30.3 ± 3.2†
Diastolic flow (ml min^{-1})	69.3 ± 6.2	48.6 ± 3.6	35.9 ± 4.8*	35.9 ± 3.9*	55.9 ± 6.3†
Diastolic CAR (unit)	12.1 ± 1.1	12.9 ± 1.5	14.5 ± 2.6	12.9 ± 2.3	12.6 ± 1.7
Mean CAR (unit)	21.6 ± 2.4	25.6 ± 2.4	26.2 ± 3.6	24.5 ± 3.0	25.4 ± 2.7
Myocardial O_2 availability (ml min^{-1})	9.91 ± 0.9	6.69 ± 0.3	5.13 ± 0.3*	4.75 ± 0.3*	6.83 ± 0.4†
Myocardial O_2 consumption (ml min^{-1})	5.9 ± 0.8	4.1 ± 0.4*	3.69 ± 0.39*	2.99 ± 0.28*	3.76 ± 0.64
Myocardial O_2 extraction (%)	59 ± 6	61 ± 6	63 ± 4	64 ± 4	60 ± 6†
Ratio availability/consumption	1.92 ± 0.35	1.81 ± 0.3	1.64 ± 0.13	1.68 ± 0.2	1.88 ± 0.19
Coronary sinus P_{O_2} (kPa)	3.27 ± 0.32	3.08 ± 0.28	2.92 ± 0.21	2.85 ± 0.23	3.13 ± 0.23

TABLE III. *Data relating to ischaemic area of myocardium before and after administration of halothane* (1% *inspired concentration*) (*mean* ± *SEM*; n = 8). * $P < 0.05$ *in comparison with control*

		Halothane			After halothane
	Control	5 min	15 min	30 min	15 min
Mean DPP (mm Hg)	38.4±4.7	35.7±6.2	32.1±7.3	31.3±6.9	35.3±7.6
Ischaemic flow (ml min^{-1} per 100 g)	29.5±6.7	20±5.4*	18±4.2*	21.6±4.1*	23.1±6.3
Ischaemic vessel resistance (unit)	97.1±8.1	162±46	172±54	160±58	135±27
Oxygen availability (ml min^{-1} per 100 g)	8.19±1.7	5.54±1.5*	4.79±1.3*	5.25±0.9*	6.84±1.6
Oxygen consumption (ml min^{-1} per 100 g)	5.48±1.3	3.83±1.12	2.87±0.7*	2.99±0.44*	4.18±0.7
Oxygen extraction (%)	65±3	66±3	61±3	60±5	61±3
Ratio availability/consumption	1.55±0.09	1.53±0.07	1.67±0.09	1.74±0.15	1.65±0.08
Coronary vein Po_2 (kPa)	2.93±0.2	2.89±0.2	3.08±0.16	3.04±0.16	2.96±0.08

In the ischaemic area there was no significant change in perfusion pressure acting through the collateral circulation during the administration of halothane or subsequent to its discontinuation (table III). Ischaemic myocardial blood flow decreased significantly in response to halothane but did not recover on discontinuing the drug (table III), and there were no significant changes in calculated ischaemic vessel resistance. Oxygen consumption in the ischaemic area decreased significantly in response to halothane, but the decrease was in proportion to the significant reduction in oxygen availability with the result that changes in oxygen extraction were not significant. Although there was a trend for the ratio of oxygen availability to oxygen consumption in the ischaemic area to increase in response to halothane and for Po_2 of blood draining from the ischaemic area to increase in response to halothane, these changes were not significant (table III).

The changes in flow and consumption in the normal and ischaemic areas of the myocardium have been compared by expressing data as a percentage of the control values (figs 1–5). Although the perfusion pressure to the ischaemic area decreased slightly in response to halothane, this change was not significant, whilst the decrease in mean arterial pressure was significant (fig. 1). However, there was no significant difference between the percentage decrease in perfusion pressure to normal or ischaemic areas (fig. 1).

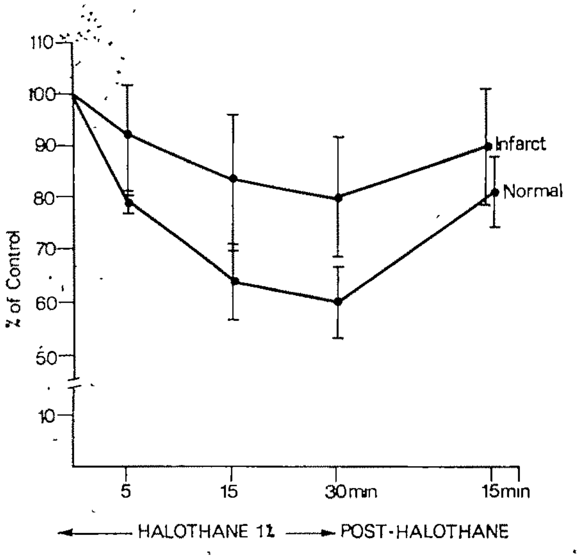


FIG. 1. Change in perfusion pressure expressed in percentages of control values before administration of halothane for normal area of myocardium (mean arterial pressure) and ischaemic area (distal perfusion pressure).

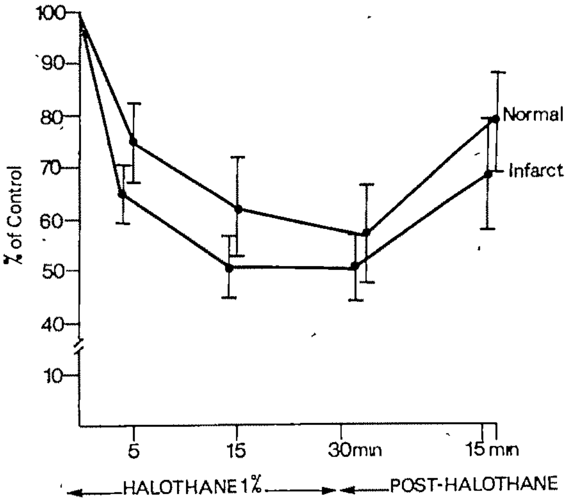


FIG. 2. Change in oxygen consumption of normal area of myocardium (normal) and ischaemic area (infarct) expressed as percentage of control values before administration of halothane.

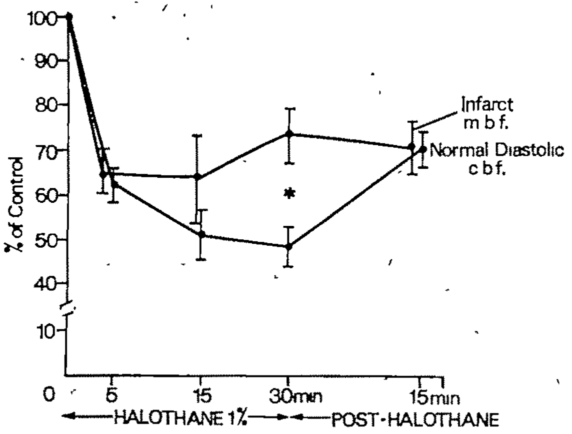


FIG. 3. Change in blood flow in normal area of myocardium and ischaemic area (infarct m.b.f.) expressed as percentage of control values before administration of halothane. * Indicates significant difference between adjacent data ($P < 0.05$).

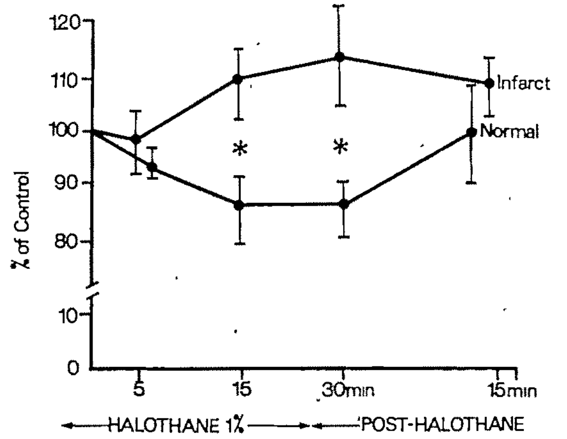


FIG. 4. Change in the ratio of oxygen availability to oxygen consumption for normal and ischaemic (infarct) areas of myocardium. * Indicates significant difference between adjacent data ($P < 0.05$).

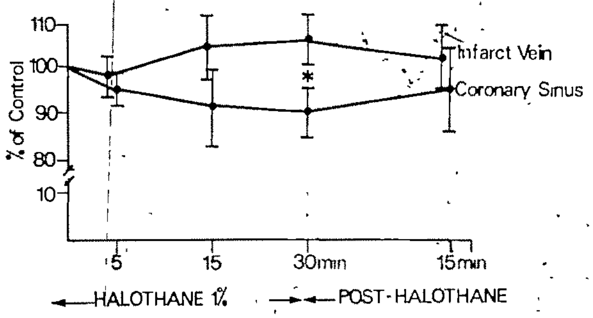


FIG. 5. Changes in venous drainage Po_2 for normal (coronary sinus) and ischaemic (coronary vein) area of myocardium. * Indicates significant difference between adjacent data ($P < 0.05$).

Oxygen consumption decreased by the same percentage in both areas (fig. 2), but the decrease in flow was significantly less in the ischaemic than in the normal area (fig. 3).

The ratio of oxygen availability to oxygen consumption is an index of the balance between oxygen supply and demand. This ratio did not change significantly in either ischaemic or normal area although there was a trend for the index to increase in the former and decrease in the latter. However, there was a highly significant difference between the percentage changes for this index in the two areas (fig. 4). This difference is reflected by the significant differences in venous drainage Po_2 from the two areas (fig. 5).

DISCUSSION

In these studies the administration of halothane was associated with a significant difference in the balance of oxygen supply to demand between the normal area of myocardium and the ischaemic area such as to favour oxygenation of the ischaemic area at the expense of the normal. This was reflected in the changes in venous drainage Po_2, which became significantly different following 30 min administration of halothane. Our study supports that of Bland and Lowenstein (1976) who found that the severity of ischaemia (as assessed by summating ST segments) was improved in canine experimental myocardial ischaemia during the administration of halothane. In their study, transient occlusion of a branch of the coronary artery was produced for a maximum period of only 12 min—a period which embraces the peak time for the development of arrhythmia after coronary artery occlusion in the dog (Marshall, Parratt and Ledingham, 1974).

Following occlusion of the left anterior descending branch in the preparation used in this study, there were marked changes in cardiac output, arterial pressure and LVEDP. Changes in pH, lactate and pyruvate concentrations in blood draining from the infarct area and changes in infarct blood flow reached a maximum within 30 min of occlusion and thereafter there was a period of stability in the haemodynamic and metabolic state (Marshall, Parratt and Ledingham, 1974). Thus, during the present study, we allowed a period of 1 h to elapse before measurements were obtained.

The significant differences in the change in oxygen supply/demand between infarct and normal area were produced by differences in flow as the changes in oxygen consumption were similar. Previous studies in this preparation of the effects of vasodilator drugs have suggested that, following acute arterial occlusion, the vessels in the infarct area are maximally dilated and unresponsive (Marshall and Parratt, 1974). Marshall and Parratt thought that the factor determining ischaemic blood flow was the "effective sub-endocardial driving pressure" (ESEDP or diastolic distal perfusion pressure minus LVEDP) (Marshall and Parratt, 1974). In the present study there was no significant correlation between ischaemic flow and mean distal perfusion pressure.

Although the changes in mean arterial pressure and distal perfusion pressure were not significantly different, distal perfusion pressure decreased to only 80% of control whilst mean arterial pressure decreased to 60% of control. It is postulated that the significant bradycardia associated with the exhibition of halothane permitted some sparing of collateral perfusion pressure during systemic hypotension.

In this investigation, LVEDP was small, indicative of the absence of cardiac failure and it did not change significantly with halothane. In the failing heart, LVEDP increases and this would diminish ESEDP, causing impairment of ischaemic area perfusion. In addition, increased LVEDP and ventricular volume are associated with an increase in ventricular wall tension which leads to increase in myocardial oxygen demand (Braunwald, 1971). Thus, although we would suggest that halothane may be beneficial for anaesthesia in the presence of myocardial ischaemia, such conclusions are applicable only to the non-failing ventricle. Extrapolation to the failing ventricle should await experimental determination of the balance between oxygen supply and demand.

Drugs with direct actions on coronary vessels may modify the degree of ischaemia in experimental myocardial infarction (Fam and McGregor, 1964). In the same preparation as that used in the present studies, dipyridamole (Marshall and Parratt, 1973a) and carbon dioxide (G. Smith and colleagues, in preparation) lead to worsening of ischaemia, whilst noradrenaline (Marshall and Parratt, 1973b) improved blood flow and reduced ischaemia. Halothane has been reported to have no action on coronary vessels (Merin, Kumazawa and Luka, 1976), to increase coronary vascular resistance (Smith et al., 1974) or to decrease it (Domenech et al., 1977). In the present study there were no significant changes in vascular resistance in either infarct or normal areas, although smaller concentrations of halothane are used than in our previous study (Smith et al., 1974). Extensive studies by Merin and colleagues (Merin, Kumazawa and Luka, 1976; Merin, Verdouw and de Jong, 1977) suggested that changes in coronary flow are almost entirely secondary to changes in ventricular function. Therefore it is unlikely that the relative improvement in oxygen supply/demand ratio in the ischaemic area relative to normal myocardium is related to any direct effect of halothane on coronary vessels.

In a previous study of halothane and the normal canine coronary circulation (Smith et al., 1974), it was concluded that, as a result of a dose-related decrease in myocardial oxygen availability, halothane may be detrimental if there is impaired myocardial perfusion in patients. This conclusion does not accord with widespread clinical experience suggesting that halothane is a well-tolerated anaesthetic agent in patients with myocardial ischaemia. In the present studies, we have used a model of acute myocardial ischaemia to measure oxygen supply and oxygen consumption and we have demonstrated that the balance between these two factors is significantly improved for the ischaemic area in comparison with the normal area in response to halothane. This lends scientific validity to the clinical impression that halothane is an appropriate and useful agent for anaesthetizing patients with myocardial ischaemia. This conclusion, however, may not be applicable in the presence of cardiac failure.

ACKNOWLEDGEMENT

This work was supported by a grant from the Scottish Hospital Endowments Research Trust (H.E.R.T. 510).

REFERENCES

Bland, J. H. L., and Lowenstein, E. (1976). Halothane-induced decrease in experimental myocardial ischaemia in the non-failing canine heart. *Anesthesiology*, **45**, 287.

Braunwald, E. (1971). Control of myocardial oxygen consumption: physiologic and clinical considerations. *Am. J. Cardiol.*, **27**, 416.

Domenech, R. J., Macho, P., Valdes, J. and Penna, M. (1977). Coronary vascular resistance during halothane anesthesia. *Anesthesiology*, **46**, 236.

Fam, W. M., and McGregor, M. (1964). Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. *Cir. Res.*, **15**, 355.

Ledingham, I. McA., McBride, T. I., Parratt, J. R., and Vance, J. P. (1970). The effect of hypercapnia on myocardial blood flow and metabolism. *J. Physiol. (Lond.)*, **210**, 87.

Marshall, R. J., and Parratt, J. R. (1973a). The effects of dipyridamole on blood flow and oxygen handling in the acutely ischaemic and normal canine myocardium. *Br. J. Pharmacol.*, **49**, 391.

—— —— (1973b). The effect of noradrenaline on blood flow and oxygen consumption in normal and ischaemic areas of myocardium. *Am. Heart J.*, **86**, 653.

—— —— (1974). Drug-induced changes in blood flow in the acutely ischaemic canine myocardium; relationship to subendocardial driving pressure. *Clin. Exp. Pharmacol. Physiol.*, **1**, 99.

—— —— Ledingham, I. McA. (1974). Changes in blood flow and oxygen consumption in normal and ischaemic regions of the myocardium following acute coronary artery ligation. *Cardiovasc. Res.*, **8**, 204.

Merin, R. G., Kumazawa, T., and Luka, N. L. (1976). Myocardial function and metabolism in the conscious dog and during halothane anesthesia. *Anesthesiology*, **44**, 402.

—— Verdouw, P. D., and de Jong, J. W. (1977). Dose-dependent depression of cardiac function and metabolism by halothane in swine (*Sus scrofa*). *Anesthesiology*, **46**, 417.

Ross, R. S., Ueda, K., Lichtlen, P. R., and Rees, R. J. (1964). Measurement of myocardial blood flow in animals and man by selective injection of radioactive inert gas into the coronary arteries. *Circ. Res.*, **15**, 28.

Smith, G., Vance, J. P., Brown, D. M., and McMillan, J. C. (1974). Changes in canine myocardial blood flow and oxygen consumption in response to halothane. *Br. J. Anaesth.*, **46**, 821.

Vance, J. P., Brown, D. M., Smith, G., and Thorburn, J. (1979). Coronary blood flow responses to hypoxia in the presence and absence of halothane. *Br. J. Anaesth.*, **51**, 193.

—— Smith, G., Thorburn, J., and Brown, D. M. (1975). The combined effect of halothane-induced hypotension and hypocapnia on canine myocardial blood flow and oxygen consumption. *Br. J. Anaesth.*, **47**, 825.

Vatner, S. F., and Smith, N. T. (1974). Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. *Circ. Res.*, **34**, 155.

L'HALOTHANE AMELIORE L'EQUILIBRE DE LA SOURCE D'OXYGENE EXIGEE DANS L'ISCHEMIE MYOCARDIAQUE EXPERIMENTALE AIGUE

RESUME

On a provoqué chez des lévriers anesthésiés au pentobarbitone un infarctus myocardiaque aigu en ligaturant la branche descendante antérieure de l'artère coronaire principale gauche. Le flux sanguin dans la zone de l'ischémie a été mesuré au moyen de l'évacuation de xénon et comparé au flux de l'artère circonflexe mesuré sur des indicateurs de flux électromagnétiques. Avec 1% d'halothane, on a obtenu une diminution d'environ 40% du flux tant dans la zone normale que dans la zone ischémique, associée à une réduction de 20% de la tension de perfusion collatérale et une baisse de 40% de la tension artérielle moyenne. La comparaison de la modification des pourcentages dans le rapport de la disponibilité/consommation d'oxygène sous l'effet de l'halothane a révélé une différence significative entre les zones normale et ischémique. La première est descendue à 91±5,02% tandis que la seconde s'est élevée jusqu'à 113±9,3% (moyenne±SEM). Ceci laisse penser que, pour un coeur sain, l'halothane améliore l'oxygénation dans les zones d'ischémie myocardiaque aigue.

HALOTHAN VERBESSERT DEN AUSGLEICH ZWISCHEN SAUERSTOFFZUFUHR UND -BEDARF BEI AKUTER EXPERIMENTALER MYOKARDISCHÄMIE

ZUSAMMENFASSUNG

Akute Myokardinfarkte wurden durch Abbinden der vorderen absteigenden Branche der linken Kranzarterie bei Windhunden hervorgerufen, die mit Pentobarbiton betaübt worden waren. Die Blutzufuhr in der Gegend der Ischämie wurde durch Xenon-Klärung gemessen und mit der Blutzufuhr in der zirkumflexen Arterie verglichen, die mit Hilfe von einem elektromagnetischen Durchflussmesser festgestellt wurde. Bei 1%-igem Halothan ergab sich eine Reduzierung von ca. 40% in der Zufuhr sowohl an ischämische wie auch an normale Gegende, in Verbindung mit einer 20% Verminderung des seitlichen Durchblutungsdrucksund einer 40% Verminderung des durchschnittlichen arteriellen Drucks. Ein Vergleich der prozentualen Änderung im Verhältnis zwischen Sauerstoffzufuhr und -verbrauch als Reaktion gegen Halothan zeigten einen bedeutenden Unterschied zwischen den ischämischen und den normalen Gegenden auf. Die ersteren stiegen auf 113±9.3% (Durchschnitt±SEM), während die letzteren auf 91±5,02% zuruckgingen. Dies deutet an, dass beim nicht-versagendem Herzen die Sauerstoffsättigung in Gegenden von akuter Myokardischämie durch Halothan verbessert wird.

EL HALOTANO MEJORA EL EQUILIBRIO DE LA PROVISION DE OXIGENO REQUERIDA EN ISQUEMIA MIOCARDIAL EXPERIMENTAL AGUDA

SUMARIO

Se indujo un infarcto miocardial agudo al ligaturar la rama descendiente anterior de la arteria coronaria principal izquierda en perros galgos anestesiados con pentobarbitona. El flujo sanguíneo en la zona de la isquemia fue medido por medio de la evacuación de Xenón y comparado con el flujo en la arteria circunfleja medido mediante flujómetros electromagnéticos. Un 1% de halotano produjo una disminución de aproximadamente 40% en el flujo tanto de la zona normal como de la zona isquémica, conjuntamente con una reducción del 20% de la presión de perfusión colateral y una reducción del 40% de la presión arterial media. La comparación del cambio en porcentaje de la relación de disponibilidad/consumo de oxígeno en respuesta al halotano reveló una diferencia significativa entre las zonas isquémica y normal. La primera aumentó hasta 113±9,3% (promedio±SEM) mientras que la última bajó hasta 91±5,02%. Esto hace pensar que, en un corazón sano, el halotano mejora la oxigenización en las zonas de isquemia miocardial aguda.

Br. J. Anaesth. (1980), 52, 585

EFFECT OF LOW CONCENTRATIONS OF HALOTHANE ON THE OXYGEN ELECTRODE

T. MAEKAWA, Y. OKUDA AND D. G. McDOWALL

SUMMARY

The effect of low concentrations of halothane dissolved in saline (equivalent to 0.34% halothane) on the oxygen electrode was examined using a multi-wire Clark type electrode, consisting of eight platinum wires, each of 15 µm tip diameter. On the first exposure of the day to saline equilibrated with halothane in 10% oxygen or air, the output of the oxygen electrode increased by 40% over 56 min. On the second and subsequent exposures the increase in output was much less, but was still 10% greater than the correct values. After immersing the electrode overnight in saline without halothane the high sensitivity to halothane was present again next morning, even if neither membrane nor electrolyte was changed.

The platinum wire oxygen microelectrode is commonly used for blood-gas analysis. It is affected by many factors in addition to oxygen (Silver, 1963; Grunewald, 1973). Severinghaus and others (1971) reported that halothane increased the output of the Clark type oxygen electrode and we observed this phenomenon during the measurement of oxygen tension on the cat cerebral cortex during halothane-induced hypotension. This paper reports bench tests of the effect of a low concentration of halothane dissolved in saline in the presence of nitrogen, 10% oxygen or air, on the output of the electrode and also the effect of 0.3% methoxyflurane under identical conditions.

METHODS

The multi-wire Clark type oxygen electrode, developed by Lübbers and his colleagues (Leniger-Follert, Lübbers and Wrabetz, 1975), was used for this investigation. It consisted of eight platinum wires, each of 15 µm diameter. The surface of the electrode was polished with Arkansas stone and lime wood and was covered with a 12-µm cellophane and a 12-µm Teflon membrane. The electrolyte consisted of potassium chloride 0.2 mol. The polarizing voltages for each wire ranged from 600 to 700 mV. The 95% response time of the electrode, including the data output system, was less than 5 s. Measurements of oxygen tension were made at 37 °C in a beaker containing 0.9% saline through which nitrogen, 10% oxygen in nitrogen, or compressed air, with or without halothane, was bubbled. In other tests the gassing mixture was 0.3% methoxyflurane in compressed air. A Drager vaporizer was used to provide halothane and a Pentec vaporizer (Cyprane Ltd) to provide 0.3% methoxyflurane. Calibration of the oxygen electrode was with a sodium sulphite zeroing solution (Radiometer Ltd) and air-equilibrated saline. This calibration procedure was carried out immediately before each measurement with or without halothane or methoxyflurane. The output from each electrode was amplified and converted to a digital signal which was recorded at 0.8-s intervals on magnetic tape. Subsequently the data were handled by a programmable calculator (Wang 720) which printed out mean Po_2 values with standard deviations for each cathode for each minute of measurement. These values were corrected by the following formula, because all electrodes could not be calibrated simultaneously:

$$Po_2 = \frac{R-Z}{R_{air}-Z} \times 0.208 P_{B\,dry}$$

where R is the reading for the test mixture; R_{air} the reading during the previous calibration with halothane-free, air-equilibrated saline; Z is the previous reading on sodium sulphite and $P_{B\,dry}$ the dry part of the barometric pressure in the mixture. The seven functioning cathodes in the electrode assembly were used at least three times for each group of measurements. The concentration of halothane in the

---

T. MAEKAWA,* M.D.; Y. OKUDA,* M.D.; D. G. McDOWALL, M.D., F.F.A.R.C.S.; Department of Anaesthesia, The University of Leeds.

* Present address: Department of Anesthesiology, Yamaguchi University Hospital, 1144 Ube-shi, Yamaguchi-ken, Japan 755.

0007–0912/80/060585–03 $01.00

© Macmillan Journals Ltd 1980

calibration solution was measured by gas chromatography (Pye Unicam 104).

RESULTS

Figure 1 shows the effect of halothane and methoxyflurane on the electrode. The $P\mathrm{o}_2$ value during the measurement in pure nitrogen without halothane increased to +0.27 kPa at 12–15 min and to +0.77 kPa at 56 min. There was no shift greater than 3.7% in the reading with 10% oxygen or air in the absence of halothane. When the electrode was exposed to 0.3% methoxyflurane in air the drift was slightly greater than in the absence of the anaesthetic gas; the maximum increase was 5.4%.

On the first exposure to halothane in air or 10% oxygen, the output of the electrode increased by more than 10% within 12 min and by more than 40% of the true value at 56 min. In pure nitrogen with halothane the output increased to 1.85 ± 0.42 kPa at 56 min (mean ± SD).

Following recalibration, the second and subsequent exposures to halothane in air or 10% oxygen increased the output by less than 10% and by less than 0.83 kPa in nitrogen.

The concentration of halothane in the calibration solution was 1.84 ± 0.11 mg% (mean ± SD). This is equivalent to a concentration in the gas phase of 0.34% halothane.

DISCUSSION

The effect of halothane in increasing the output of the platinum oxygen electrode has been reported previously by Severinghaus and others (1971) and by McHugh, Epstein and Longnecker (1979). Severinghaus studied concentrations of 33% whilst McHugh and colleagues used 1% halothane. The present results show that even with a concentration as low as 0.34% there was an appreciable effect on the oxygen electrode output. Dent and Netter (1976) reported that halothane had no effect on the Clark-type oxygen electrode when PTFE was used for the membrane. Since PTFE is basically the same material as used in the present experiments, we are unable to explain the discrepancy in the findings. As regards the volatile anaesthetics, McHugh, Epstein and Longnecker (1979) showed that 2% enflurane did not increase the output of the oxygen electrode and in the present results it has been shown that methoxyflurane had only a small effect.

There have been no previous comments on the variation of the effect of halothane in relation to the number of exposures of the electrode. In the present

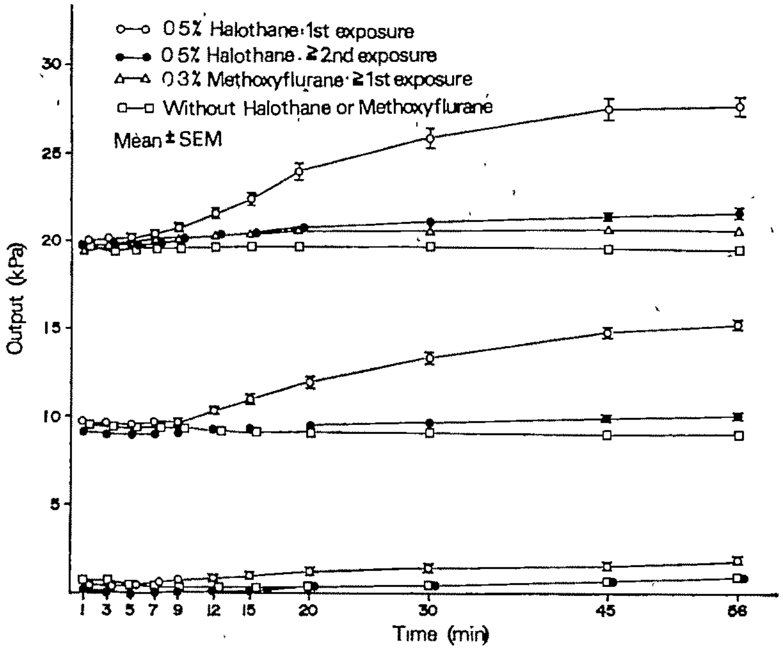


FIG. 1. The mean outputs of the oxygen electrode during exposure to nitrogen, 10% oxygen in nitrogen and air, with and without halothane or methoxyflurane. The results were obtained by placing the electrode in a beaker containing saline at 37 °C, through which the gases and vapours were bubbled.

study we have observed that the first exposure of the day has the greatest effect and we conclude that the change produced by halothane at the platinum surface occurs mainly during this first exposure and is only slowly reversible.

Caution is necessary in extrapolating these results to the conditions of blood-gas measurement in patients receiving halothane, since the conditions of calibration and the duration of exposure to halothane were quite different. Of course, with the greater halothane solubility in blood, more halothane would be present in a blood sample, but this should not alter the effect on the oxygen electrode, which will be determined by the tension of halothane in the sample and the halothane solubility of the electrode's electrolyte. Given the pharmacokinetics of halothane, the tension equivalent to 0.34% is in the range of blood values present during light surgical anaesthesia.

From the above results it may be concluded that even low concentrations of halothane have an effect on the oxygen electrode, especially when the electrode has not been exposed to the agent for some hours. However, with the exception of such "first" samples, the effect will be small for measurements made within 5 min of introducing the sample into the electrode.

ACKNOWLEDGEMENT

This study was supported by the Medical Research Council.

REFERENCES

Dent, J. G., and Netter, K. J. (1976). Errors in oxygen tension caused by halothane. *Br. J. Anaesth.*, **48**, 195.

Grunewald, W. (1973). Accuracy and errors of the Po_2 measurement by means of the platinum electrode and its calibration *in vivo*; in *Modern Techniques in Physiological Science* (eds R. Kaufmann and J. F. Gross), p. 309. New York and London: Academic Press.

Leniger-Follert, E., Lübbers, D. W., and Wrabetz, W. (1975). Regulation of local Po_2 of the brain cortex at different arterial O_2 pressures. *Pfluegers Arch.*, **359**, 89.

McHugh, R. D., Epstein, R. M., and Longnecker, D. E. (1979). Halothane mimics oxygen in oxygen microelectrodes. *Anesthesiology*, **50**, 47.

Severinghaus, J. W., Weiskopf, R. B., Nishimura, M., and Bradley, A. F. (1971). Oxygen electrode errors due to polarographic reduction of halothane. *J. Appl. Physiol.*, **31**, 640.

Silver, I. (1963). A simple microelectrode for measuring Po_2 in gas or fluid. *Med. Electron. Biol. Eng.*, **1**, 547.

EFFET DES FAIBLES CONCENTRATIONS D'HALOTHANE SUR L'ELECTRODE D'OXYGENE

RESUME

On a étudié à l'aide d'une électrode multi-fils du type Clark, comportant huit fils de platine ayant chacun une pointe d'un diamètre de 15 µm, l'effet qu'ont, sur l'électrode d'oxygène, les faibles concentrations d'halothane dissout dans du sérum physiologique (équivalent à 0,34% d'halothane). Lors de la première exposition de la journée au sérum physiologique équilibré avec de l'halothane dans 10% d'oxygène ou d'air, le dégagement de l'électrode d'oxygène a augmenté de 40% en 56 mn. Lors de la seconde exposition et des expositions suivantes, l'augmentation du dégagement a été nettement moindre, mais elle a tout de même été de 10% supérieure aux valeurs témoins. Après avoir plongé l'électrode pendant toute la nuit dans du sérum physiologique ne contenant pas d'halothane, la forte sensibilité à l'halothane était à nouveau présente le lendemain matin, même sans avoir effectué aucun changement de membrane ou d'électrolyte.

DIE AUSWIRKUNG VON GERINGEN KONZENTRATIONEN VON HALOTHAN AUF DIE SAUERSTOFF-ELEKTRODE

ZUSAMMENFASSUNG

Die Auswirkung von geringen Konzentrationen von in einer physiologischen Kochsalzlosung aufgelöstem Halothan (entspricht 0,34% Halothan) auf die Sauerstoffelektrode wurde untersucht. Es wurde dabei eine mehrdrahtige Clark-Elektrode bestehend aus 8 Platindrähten von je 15 µm Spitzendurchmesser verwendet. Als die Elektrode zum ersten Mal am Tag an einer mit Halothan ausgeglichenen Lösung von physiologischem Kochsalz in 10%-igem Sauerstoff oder Luft ausgesetzt wurde, stieg die Abgaberate der Sauerstoffelektrode über einen Zeitraum von 56 Minuten um 40% an. Bei der zweiten und bei weiteren Aussetzungen am gleichen Tage stieg die Abgaberate viel weniger an, lag aber immer noch um 10% höher als die richtigen Werte. Nachdem die Elektrode über Nacht in einer physiologischen Kochsalzlösung ohne Halothan gestanden hatte, zeigte sich wieder am nächsten Morgen dieselbe Empfindlichkeit gegen Halothan, selbst wenn weder die Membran noch der Elektrolyt ausgewechselt worden war.

EFECTO DE BAJAS CONCENTRACIONES DE HALOTANO SOBRE EL ELECTRODO DE OXIGENO

SUMARIO

Se procedió al examen del efecto de bajas concentraciones de halotano disuelto en solución salina (equivalente de halotano al 0,34%) sobre el electrodo de oxígeno, al usar un electrodo Clark multi-alámbrico que consistía en ocho alambres de platino de 15 µm de diámetro de punta cada uno. En la primera exposición del día a la solución salina equilibrada con halotano en oxígeno al 10% o en el aire, el rendimiento del electrodo de oxígeno aumentó en un 40% sobre un periodo de 56 min. En la segunda exposición y demás exposiciones, el aumento del rendimiento fue mucho menor, pero era aún mayor en un 10% con respecto a los valores correctos. Después de sumergir el electrodo durante la noche en solución salina sin halotano, se notó también a la mañana siguiente la alta sensibilidad al halotano, aún sin haber cambiado de membrana o de electrólito.

Br. J. Anaesth. (1980), **52**, 589

EFFECT OF BARICITY ON SPINAL ANAESTHESIA WITH AMETHOCAINE

D. T. Brown, J. A. W. Wildsmith, B. G. Covino and D. B. Scott

SUMMARY

Amethocaine 1% solution was mixed with equal volumes of water, 0.9% saline or 10% dextrose to prepare respectively, hypobaric, isobaric and hyperbaric solutions which were compared for intradural spinal anaesthesia in 60 patients. Thirty patients received 10 mg and 30 patients received 15 mg of amethocaine. Injections were made with the patients in the lateral recumbent position and the operating table was horizontal during and after injection. Equal numbers of patients and equal numbers of males and females received hypobaric, isobaric and hyperbaric solutions. The mean spread of analgesia after the hyperbaric solution was five dermatomes greater than after the other two solutions, but the extent of analgesia was not significantly different whether amethocaine 10 mg or 15 mg was injected. The mean duration of analgesia after the hyperbaric solution was 285 min compared with 332 min and 360 min after the isobaric and hypobaric solutions respectively. The mean duration of analgesia after amethocaine 15 mg was significantly greater than after 10 mg.

Factors which are believed to influence the extent and duration of intradural spinal anaesthesia include gravity and the baricity, volume and concentration of the injected local anaesthetic solution (Greene, 1969; Lee and Atkinson, 1978).

Solutions for spinal anaesthesia may be classified as hyperbaric, isobaric or hypobaric depending on whether they are heavier than, of equal weight to, or lighter than cerebrospinal fluid. Barker (1907) used glass tubes shaped to reproduce the curvature of the vertebral column to demonstrate that hyperbaric anaesthetic solutions spread rapidly under the influence of gravity and collected in the lowest part of the glass tube while isobaric solutions remained localized at the site of injection. However, the spinal anaesthetic blocks produced in patients by solutions of different specific gravity have never been compared in a controlled trial. This investigation was designed to compare the clinical effects of spinal anaesthesia with hyperbaric, isobaric and hypobaric amethocaine at doses of 10 mg and 15 mg.

PATIENTS AND METHODS

Patients

Patients who were to have spinal anaesthesia for elective gynaecological or general surgery to the lower trunk or legs were investigated. They were accepted for study if they consented to have the anaesthetic blockade assessed and if there was no evidence of hypovolaemia, intra-abdominal distension or infection of the lumbar area. Thirty adult men and 30 adult women were studied. The male patients were older, taller and heavier than the female patients, but there were no other statistically significant differences between the groups (table I).

Preparation of amethocaine solutions

A 1% solution of amethocaine (Pontocaine, Winthrop Laboratories) has a specific gravity (sp. gr.) between 1.0060 and 1.0074 and is isobaric compared with cerebrospinal fluid (sp. gr. 1.0063–1.0075). This solution was mixed with an equal volume of water, 0.9% sodium chloride solution or 10% dextrose solution to produce 0.5% solutions of amethocaine that were hypobaric (sp. gr. 1.0037), isobaric (sp. gr. 1.0069) or hyperbaric (sp. gr. 1.0215). The solutions were drawn from autoclaved ampoules and mixed in a syringe immediately before injection.

Experimental design

Fifteen men and 15 women were each given amethocaine 10 mg (2 ml) and 15 men and 15 women were each given 15 mg (3 ml). Within each group of 15 patients, five received hypobaric solution, five received isobaric solution and five received hyperbaric solution. The specific gravity of the solution to be used was obtained from a predetermined randomized code known only to the

---

D. T. Brown, M.B., Ch.B., F.F.A.R.C.S.; J. A. W. Wildsmith, M.B., Ch.B., F.F.A.R.C.S.; D. B. Scott, M.D., F.R.C.P.E., F.F.A.R.C.S.; Department of Anaesthesia, The Royal Infirmary, Edinburgh EH3 9YW. B. G. Covino, M.D., Department of Anesthesia, University of Massachusetts Medical Center, Worcester, Ma 01605, U.S.A.

0007-0912/80/060589-08 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Ages, weights and heights of groups of patients receiving intradural spinal anaesthesia with amethocaine in vehicles of different specific gravity (mean ± SEM). The first section compares the differences between groups of different specific gravity, the second section compares the differences between the 10-mg and the 15-mg groups and the third section compares the differences between males and females. n.s. = not significant* ($P > 0.05$); **$0.01 > P$

Group	Age (yr)	Weight (kg)	Height (cm)
(20 patients in each group)			
Hyperbaric	46.40	65.16	164.60
	3.28	1.97	1.89
	n.s.	n.s.	n.s.
Isobaric	49.20	63.82	166.67
	3.81	2.08	2.17
	n.s.	n.s.	n.s.
Hypobaric	54.10	68.85	168.55
	3.75	2.26	2.14
	n.s.	n.s.	n.s.
Hyperbaric	46.40	65.16	164.60
	3.28	1.97	1.89
(30 patients in each group)			
10 mg	48.07	67.86	167.83
	2.79	1.76	1.61
	n.s.	n.s.	n.s.
15 mg	51.73	64.03	165.55
	3.14	1.66	1.73
(30 patients in each group)			
Males	58.03	68.15	173.11
	3.19	1.76	1.42
	**	n.s.	**
Females	41.77	63.74	160.27
	1.77	1.64	0.90

anaesthetist making the injection. Neither the patient nor the investigator who assessed the clinical effects of the blocks knew the specific gravity of the solutions being used.

Anaesthetic procedure

After premedication, a lumbar puncture was made with either a 22- or a 25-gauge needle using a standard midline approach with the patient in the lateral recumbent position on a horizontal operating table. The interspace between the 3rd and 4th lumbar spines was used unless difficulty was encountered, when the 2nd or 4th interspace was used. Once a free flow of cerebrospinal fluid was obtained, amethocaine solution either 10 mg or 15 mg was injected over 15 s without barbotage. Immediately after the injection the patients were turned to lie supine with the legs extended, the operating table being kept horizontal. Assessments of the spinal block were made during the first 20 min after injection and the patients were then given thiopentone i.v. To ensure rapid recovery after operation general anaesthesia was maintained at a light level either with increments of thiopentone or with nitrous oxide supplemented occasionally by halothane.

Measurements

Arterial pressure and heart rate were recorded before the patient was positioned for lumbar puncture and at 5-min intervals after injection of the anaesthetic (table II). At 5-min intervals after injection, but before the start of the operation, measurements were made of the cephalad extent of analgesia and anaesthesia and motor weakness in the legs were assessed. Analgesia was defined as the inability to appreciate pinprick, anaesthesia as inability to appreciate touch. After the spread of anaesthesia was complete the patient underwent surgery. Similar measurements were made after operation at 1-h intervals until the effects of the anaesthetic had worn off completely and the patients felt that their legs had returned to normal. From these measurements data on the onset, spread and duration of anaesthesia were obtained (tables III, IV). The mean values of the data from the different groups were calculated. The significance of the difference was determined using a Student's *t* test.

RESULTS

Onset

The mean interval until analgesia was detectable in the thoracic dermatomes was 5.8 ± 0.6 min after hyperbaric, 8.5 ± 1.4 min after isobaric and 10.3 ± 1.6 min after hypobaric amethocaine, the last being significantly longer than after hyperbaric amethocaine. The mean interval until the spread of analgesia was maximal was 12.0 ± 0.8 min after hyperbaric, 13.5 ± 1.0 min after isobaric and 14 ± 1.2 min after hypobaric solution, but these times did not differ significantly. The onset time and the mean time taken to achieve the maximum extent of analgesia showed no significant difference between males and females. After amethocaine 10 mg the mean time to maximum spread of analgesia was 3 min less than after amethocaine 15 mg.

Spread

The maximum height of analgesia produced by each injection is shown in figure 1 and the mean maximum height of analgesia produced by each specific gravity of amethocaine is shown in figure 2. The mean maximum spread of analgesia (loss of sensation to pinprick) after hyperbaric amethocaine

TABLE II. *Mean arterial pressures (mm Hg) and heart rates (beat min⁻¹) before and 10 min after intradural amethocaine (mean ± SEM). The first section compares the differences between groups of different specific gravity, the second section compares the differences between the 10-mg and the 15-mg groups and the third section compares the differences between males and females. n.s. = not significant* ($P > 0.05$); * $0.05 > P > 0.01$; ** $0.01 > P$

	Systolic art. pressure		Diast. art. pressure		Heart rate	
Group	Before	After	Before	After	Before	After
(20 patients in each group)						
Hyperbaric	125.85	97.25	79.20	55.50	76.00	80.10
	3.83	5.17	2.38	3.73	3.36	4.63
	n.s.	*	n.s.	**	n.s.	n.s.
Isobaric	127.65	116.25	78.15	70.25	80.00	81.70
	4.62	7.30	3.32	3.80	3.07	3.64
	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Hypobaric	136.00	124.50	81.15	73.75	83.15	85.50
	7.05	7.83	3.20	4.34	2.74	3.53
	n.s.	**	n.s.	**	n.s.	n.s.
Hyperbaric	125.85	97.25	79.20	55.50	76.00	80.10
	3.83	5.17	2.38	3.73	3.36	4.63
(30 patients in each group)						
10 mg	131.23	116.83	78.83	69.33	84.87	78.67
	5.84	7.07	2.48	4.14	3.08	3.03
	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
15 mg	126.33	108.50	75.50	63.50	82.30	87.20
	4.46	4.46	3.09	2.63	2.69	3.04
(30 patients in each group)						
Male	142.67	122.50	84.50	73.67	76.33	73.07
	5.10	7.00	2.53	3.96	2.53	2.54
	**	**	*	**	**	**
Female	114.90	102.83	69.83	59.17	90.83	92.80
	3.88	3.89	2.40	2.31	2.61	2.55

(17.5 dermatomes) was significantly greater than that after isobaric amethocaine (13.5) and after hypobaric amethocaine (12.2). The spread of analgesia after amethocaine 15 mg, however, was not significantly different from that after 10 mg and in male patients it was not significantly different from the spread in females, despite their differences in height and weight. The spread of anaesthesia (loss of sensation to touch) after hyperbaric amethocaine was 16.5 dermatomes, after isobaric amethocaine 12.2 and after hypobaric amethocaine 10.6 dermatomes.

Motor

Nineteen of the 20 patients who received heavy solutions had complete motor blockade of the lower limbs. Only one patient who received a heavy solution had poor motor blockade with analgesia that did not spread above the level of the knees. The isobaric solutions produced complete motor blockade in 16 of 20 patients including one who had analgesia to T12 but was still able to elevate his heels from the bed and bend his knees. Hypobaric solutions produced the least motor blockade, only 11 of 20 patients being completely unable to move the legs. Two patients who were still able to move the legs had analgesia extending to the thoracic dermatomes. The frequency of motor block after hypobaric solutions was significantly less than after hyperbaric solutions.

Regression and duration

The mean time until regression of analgesia was detected was 153.0 ± 9.9 min after hyperbaric solutions, 162.5 ± 10.3 min after isobaric solutions, but was 199.1 ± 15.9 min after hypobaric solutions. The mean interval until no further analgesia was detectable was 285.4 ± 13.2 min after heavy solutions—significantly shorter than 332.0 ± 15.7 min after isobaric solutions and 360.2 ± 12.3 min after hypobaric solutions. Similarly, the mean duration of the motor blocks was 239.5 ± 13.1 min for hyperbaric solutions—significantly shorter than 308.7 ± 19.1 min with isobaric and 290.6 ± 18.3 min with hypobaric

TABLE III. *Onset and spread of effect after intradural spinal anaesthesia with amethocaine (mean ± SEM). Onset is the interval until analgesia was first detected above either inguinal ligament. This level of analgesia was not reached in all patients. †The number who were analgesic is shown in parentheses in the first column. Time to maximum is the interval until no further cephalad spread of analgesia was detected. The first section compares the differences between groups of different specific gravity, the second compares the differences between the 10-mg and the 15-mg groups and the third section compares the differences between males and females. n.s. = not significant* ($P > 0.05$); *$0.05 > P > 0.01$; ** $0.01 > P$

Group	Onset (min)	Time to maximum (min)	Extent of analgesia (dermatome)	Extent of anaesthesia (dermatome)
(20† patients in each group)				
Hyperbaric	5.79	12.00	17.50 T5.5	16.45 T6.6
	(19) 0.58	0.84	0.65	0.68
	n.s.	n.s.	**	**
Isobaric	8.53	13.50	13.48 T9.5	12.15 T10.8
	(17) 1.41	0.97	0.79	0.63
	n.s.	n.s.	n.s.	n.s.
Hypobaric	10.33	14.00	12.18 T10.8	10.63 T12.4
	(15) 1.58	1.24	0.92	0.83
	*	n.s.	**	**
Hyperbaric	5.79	12.00	17.50 T5.5	16.45 T6.6
	(19) 0.58	0.84	0.65	0.68
(30† patients in each group)				
10 mg	6.96	11.67	14.05 T8.9	12.88 T10.1
	(23) 0.93	0.77	0.82	0.80
	n.s.	*	n.s.	n.s.
15 mg	8.93	14.67	14.45 T8.5	13.32 T9.7
	(28) 1.07	0.83	0.62	0.68
(30† patients in each group)				
Male	8.57	13.00	14.62 T8.4	13.37 T9.6
	(28) 1.12	0.95	0.72	0.73
	n.s.	n.s.	n.s.	n.s.
Female	7.39	13.33	14.15 T8.8	12.83 T10.2
	(23) 0.88	0.73	0.81	0.76

solutions. Amethocaine 10 mg also had a significantly shorter duration of action, providing detectable analgesia for only 306.4 ± 11.9 min compared with 345.3 ± 12.2 min after 15 mg. The duration of action did not differ significantly between males and females.

Arterial pressures and heart rates

Although the pre-anaesthetic arterial pressures of the groups had not differed significantly, the average arterial pressure of the patients 10 min after hyperbaric amethocaine (97/56 mm Hg) was significantly less than after both isobaric amethocaine (116/70 mm Hg) and hypobaric amethocaine (125/74 mm Hg). There was, however, no significant difference between the heart rates of the groups. There was no significant difference in arterial pressures and heart rates of the group receiving 10 mg compared with those receiving 15 mg. The differences in arterial pressure and heart rate between males and females reflected those differences existing before anaesthesia.

DISCUSSION

The object of the investigation was to determine the manner in which the specific gravity of an intradural spinal anaesthetic solution influenced the anaesthesia it produced. The anaesthesia following amethocaine 10 mg and 15 mg and the anaesthesia in males and females were compared also.

The spread of analgesia after hyperbaric solutions of amethocaine was five dermatomes higher than after isobaric and hypobaric solutions and, consequently, the decreases in arterial pressure of the group receiving hyperbaric solution were significantly greater than those in the groups receiving either of

TABLE IV. *Motor block, regression and duration of effect after intradural spinal anaesthesia with amethocaine (mean ± SEM). Motor block shows the proportion of patients whose legs became completely paralysed. The start of regression is the mean interval until analgesia was first detected as less than maximum and thoracic regression is the interval until no analgesia was detectable above either inguinal ligament. Duration of analgesia is the mean interval until no analgesia was detectable on the legs, motor duration was the mean interval until the patients could raise their legs from the bed and subjective duration was the mean interval until the patients thought that the anaesthetic had completely worn off and the legs felt completely normal again. The first section compares the differences between groups of different specific gravity, the second section compares the differences between the* 10-*mg and the* 15-*mg groups and the third section compares the differences between males and females. n.s. = not significant* ($P > 0.05$); * $0.05 > P > 0.01$; ** $0.01 > P$

Group	Motor block	Regression		Duration		
		Start	Thoracic	Analgesia	Motor	Subjective
(20 patients in each group)						
Hyperbaric	0.95	152.95	225.55	285.35	239.50	306.45
	0.05	9.91	12.81	13.17	13.12	13.07
	n.s.	n.s.	n.s.	*	**	**
Isobaric	0.80	162.45	232.35	332.00	308.70	373.60
	0.09	10.26	21.17	15.70	19.06	17.23
	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Hypobaric	0.55	199.10	231.80	360.20	290.55	385.05
	0.11	15.93	17.92	12.32	18.31	13.53
	**	*	n.s.	**	*	*
Hyperbaric	0.95	152.95	225.55	285.35	239.50	306.45
	0.05	9.91	12.81	13.17	13.12	13.07
(30 patients in each group)						
10 mg	0.77	175.00	205.96	306.37	260.57	340.70
	0.08	11.61	11.92	11.89	16.16	14.32
	n.s.	n.s.	*	*	n.s.	n.s.
15 mg	0.77	168.00	248.93	345.33	298.60	369.37
	0.08	9.56	14.41	12.16	12.38	14.33
(30 patients in each group)						
Male	0.73	162.70	238.75	339.37	295.90	357.23
	0.08	8.07	15.19	10.72	14.15	6.77
	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Female	0.80	180.30	210.35	312.33	263.27	352.83
	0.07	12.51	11.97	13.71	14.86	15.50

the other solutions. The duration of action of the hyperbaric solutions was about 1 h shorter than the duration of the other two solutions.

When a patient lies horizontally with extended legs, the highest part of the spinal column is the third lumbar vertebra at the apex of the lumbar curvature and the lowest part is between the 5th and 6th thoracic vertebrae in the hollow of the thoracic curvature. The anaesthetic solutions were injected in the lumbar region at the highest point of the spinal column. The mean height of analgesia was the 5th thoracic dermatome after hyperbaric solutions, the 10th thoracic dermatome after isobaric solutions and the 11th thoracic dermatome after hypobaric solutions. Therefore, the hyperbaric solutions could spread under the influence of gravity into the hollow of the thoracic curve while isobaric and hypobaric solutions remained nearer to the site of injection. This confirms that the spread of spinal anaesthetic solutions in cerebrospinal fluid within the spinal column is similar to the spread within the "glass spines" (Barker, 1907). In one patient injection of heavy amethocaine produced analgesia restricted to the lower lumbar and sacral segments. The solution was injected between the 4th and 5th lumbar vertebrae and was probably deposited on the sacral side of the lumbar curvature rather than at the apex and so was unable to run into the thoracic hollow.

The hypobaric and isobaric solutions produced less complete motor blocks than did hyperbaric solutions. After hyperbaric solutions 19 of 20 patients were completely unable to move the legs, the

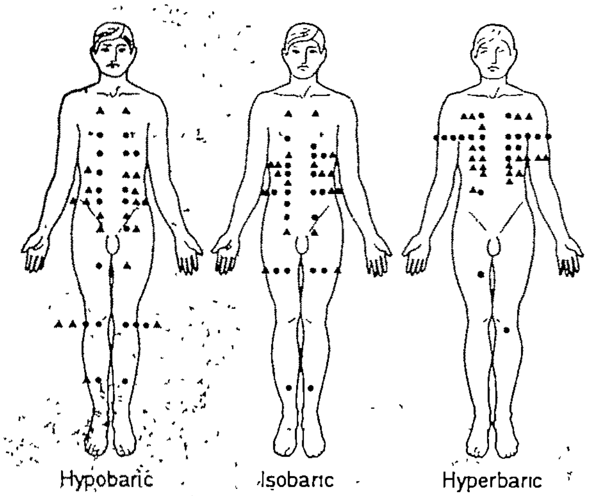


FIG. 1. Each symbol marks the most cephalad spread of analgesia (at 15 min), on both the left and the right sides, that followed a spinal injection of amethocaine. There were 20 injections in each group. Ten injections in each group contained amethocaine 10 mg (●) and 10 injections contained 15 mg (▲).

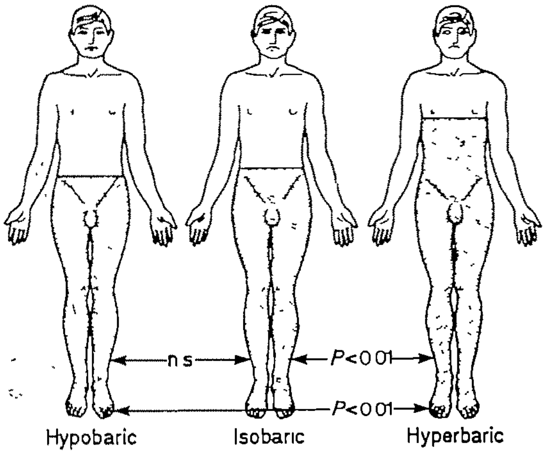


FIG. 2. Mean of the maximum heights of analgesia produced by each specific gravity of amethocaine.

exception being the patient in whom amethocaine spread only into the spinal curve. After isobaric solutions, however, only 16 of 20 patients were completely unable to move the legs and after hypobaric solutions only 11 of 20 patients. Therefore the hyperbaric amethocaine solutions spread further than the other two solutions and did so in sufficient concentration to produce complete sensory and motor block.

The duration of action of the amethocaine was affected by the vehicle in which it was injected. It is of interest that, while the hyperbaric solutions produced more widespread blockade, their mean duration was shorter than with the other two solutions. This could be a result of the greater spread of the solutions allowing more rapid uptake into the blood from the anaesthetized nervous tissue (Greene, 1969). The isobaric solutions spread much less extensively and greater concentrations of amethocaine may have been present at the site of injection thus increasing the mean duration of action. However, against this the quality of block as judged by motor paralysis was more profound with the hyperbaric solution. Nevertheless, the hypobaric solutions, which blocked the fewest dermatomes, took 45 min longer to start to regress than the hyperbaric solutions. The mean duration of analgesia after amethocaine 15 mg was 45 min longer than after amethocaine 10 mg because, as the spread of the solution was similar in extent, 15 mg presumably caused a greater concentration in the nerves and spinal cord than 10 mg. Although the method of determining duration (hourly examinations after operation) lacks precision, the data on duration of analgesia, duration of motor block and the patient's opinion on duration of action were consistent.

The finding that there was no difference between the mean height of analgesia after amethocaine 10 mg (2 ml) and the mean height after 15 mg (3 ml) was surprising. Most anaesthetists believe that increasing the dose or volume of an intradural spinal anaesthetic solution increases the extent of the blockade. However, there was no evidence from this study that the height of analgesia was dose-related. A similar result was found during a comparison of amethocaine with bupivacaine for spinal anaesthesia (Pflug, Aasheim and Beck, 1976), the dose of hyperbaric amethocaine having only a small effect on the spread of anaesthesia. Nolte and Stark (1976), using isobaric bupivacaine for spinal anaesthesia, found that an increase in dose was not followed by a larger segmental spread of analgesia, although the duration of analgesia was prolonged significantly.

The spread of analgesia produced by the hypobaric solutions used in the present study was similar to the spread produced by the isobaric solutions, but their clinical usefulness was more limited because only 11 of 20 patients had a successful motor block and adequate anaesthesia. However, the technique we used cannot be compared directly with the usual hypobaric technique for spinal anaesthesia (Lund and

Rumball, 1947) in which up to 20 ml of 0.1% solution of amethocaine is injected.

Spinal anaesthesia with isobaric anaesthetic solutions is not popular (Lund and Cwik, 1968). However, this study indicates that they may have desirable clinical features. The mean height of analgesia was the 10th thoracic dermatome, which provides a useful block for operations on the legs, perineum or groin. Furthermore, they reduce the chance of spread to the upper thoracic region and the consequent decrease in arterial pressure that would be undesirable in some patients. The duration of action after isobaric solutions is longer than after hyperbaric solutions. Increasing the duration of anaesthetic action by using larger doses of anaesthetic without the risk of excessively high blockade may be possible, but further work is required to determine the dose range over which this observation is true.

While it seems that the differences between hypobaric, isobaric and hyperbaric solutions are related to their density and the effects of gravity, the contribution of viscosity should not be ignored. Solutions made hyperbaric by the addition of dextrose are considerably more viscous than hypobaric or isobaric solutions which are prepared in water or saline. Thus there may be less tendency for the drug to diffuse into and become diluted by the cerebrospinal fluid, thus allowing it to spread further in a relatively concentrated state. The difference in the anaesthetic pattern seen with hyperbaric solutions could be related to this.

ACKNOWLEDGEMENTS

The specific gravities of the amethocaine mixtures used in this investigation were measured in the laboratories of Astra Pharmaceutical Products Inc., Worcester, Ma, U.S.A.

We thank our colleagues in surgery and gynaecology and the theatre and ward staff whose co-operation made the study possible.

REFERENCES

Barker, A. E. (1907). A report on experiences with spinal anaesthesia in 100 cases. *Br. Med. J.*, **1**, 665.

Greene, N. M. (1969). *Physiology of Spinal Anaesthesia*, 2nd edn, p. 1. Baltimore: The Williams and Wilkins Co.

Lee, J. A., and Atkinson, R. S. (1978). *Sir Robert Macintosh's Lumbar Puncture and Spinal Analgesia—Intradural and Extradural*, 4th edn, p. 134. Edinburgh, London and New York: Churchill Livingstone.

Lund, P. C., and Cwik, J. C. (1968). Modern trends in spinal anaesthesia. *Can. Anaesth. Soc. J.*, **15**, 118.

—— Rumball, A. C. (1947). Hypobaric pontocaine spinal anesthesia—1640 consecutive cases. *Anesthesiology*, **8**, 181.

Nolte, H., and Stark, P. (1976). The dose-effect-ratio of isobaric bupivacaine in spinal analgesia. *Reg. Anaesth.*, **2**, 1.

Pflug, A. E., Aasheim, G. M., and Beck, H. A. (1976). Spinal anesthesia: Bupivacaine versus tetracaine. *Anesth. Analg. (Cleve.)*, **55**, 489.

EFFET DE LA DENSITE SUR L'ANESTHESIE RACHIDIENNE PRODUITE PAR L'AMETHOCAINE

RESUME

On a mélangé une solution d'améthocaïne à 1% à des volumes égaux d'eau, de sérum à 0,9% ou de dextrose à 10% pour préparer des solutions hypobares, isobares et hyperbares que l'on a comparées lors de l'anesthésie rachidienne intradurale de 60 patients. Trente d'entre-eux ont reçu 10 mg d'améthocaïne, alors que 30 autres patients en ont reçu 15 mg. Les injections ont été faites dans la position latérale couchée et la table d'opération est restée horizontale pendant et après l'injection. Un nombre égal de malades—hommes et femmes—a reçu des solutions hypobares, isobares et hyperbares. La transmission moyenne de l'analgésie après la solution hyperbare a été de cinq dermatomes plus élevée qu'après les deux autres solutions, mais la profondeur de l'analgésie n'a pas été très différente, que les doses d'améthocaïne injectées aient été de 10 mg ou de 15 mg. La durée moyenne de l'analgésie après la solution hyperbare a été de 285 mn contre 332 mn et 360 mn après les solutions isobares et hypobares, respectivement. La durée moyenne de l'analgésie après 15 mg d'améthocaïne a été nettement plus grande qu'après une dose de 10 mg.

DIE AUSWIRKUNG VON BARIZITÄT AUF LUMBALANÄSTHESIE MIT AMETHOCAINE

ZUSAMMENFASSUNG

Eine 1%-ige Amethocaine-Lösung wurde mit gleichen Anteilen von Wasser, 0,9%-iger physiologischer Kochsalzlosung oder 10%-iger Dextrose gemischt, um hypobarische, isobarische und hyperbarische Lösungen herzustellen, die zwecks intraduraler Lumbalanästhesie in 60 Patienten verglichen wurden. Von den 60 Patienten erhielten 30 10 mg Amethocaine und 30 15 mg Amethocaine. Bei den Injektionen lagen die Patienten in der Sietenlage und der Operationstisch war wahrend und nach den Injectionen horizontal. Die hypobarischen, isobarischen und hyperbarischen Lösungen wurden in die gleiche Anzahl Patienten injiziert, jeweils gleichmässig auf die Geschlechter verteilt. Die durchschnittliche Verteilung von Analgesie nach der hyperbarischen Losung war um 5 Dermatome grösser als nach den beiden anderen Lösungen, aber ob 10 mg oder 15 mg Amethocaine verabreicht wurde, war im Ausmass der Analgesie kein bedeutender Unterschied festzustellen. Die durchschnittliche Dauer der Analgesie nach der hyperbarischen Lösung war 285 Minuten, verglichen mit 332 Minuten bzw. 360 Minuten für die isobarische bzw. die hypobarische Losung. Die durchschnittliche Dauer der Analgesie nach 15 mg Amethocaine war bedeutend grösser als nach 10 mg.

EFECTO DE LA BARICIDAD SOBRE LA ANESTESIA ESPINAL CON AMETOCAINA

SUMARIO

Se mezcló una solución de ametocaina al 1% con iguales volúmenes de agua, de solución salina al 0,9% o de dextrosa al 10% para preparar, respectivamente, soluciones hipobárica, isobarica e hiperbárica que fueron objeto de una comparación para anestesia espinal intradural en 60 pacientes. Se administró 10 mg de ametocaina a treinta pacientes y 15 mg a 30 pacientes. Se dieron las inyecciones a los pacientes en posición recostada lateral y la mesa de operación se encontraba horizontal durante y después de la inyección. Se administraron soluciones hipobáricas, isobáricas e hiperbáricas a un número igual de pacientes así como a igual número de hombres y mujeres. La dispersión media de la analgesia después de la solución hiperbárica fue cinco dermatomas mayor que con las otras dos soluciones, pero la extensión de la analgesia no difirió de manera significativa según se inyectó 10 mg ó 15 mg. La duración media de la analgesia después de la solución hiperbárica fue de 285 min, en comparación con 332 min y 360 min después de las soluciones isobárica e hipobárica, respectivamente. La duración media de la analgesia después de 15 mg de ametocaina fue significativamente mayor que con 10 mg.

Br. J. Anaesth. (1980), **52**, 597

PLASMA ATROPINE CONCENTRATIONS DETERMINED BY RADIOIMMUNOASSAY AFTER SINGLE-DOSE I.V. AND I.M. ADMINISTRATION

L. BERGHEM, U. BERGMAN, B. SCHILDT AND B. SÖRBO

SUMMARY

The plasma concentrations of atropine following i.v. or i.m. administration to surgical patients were determined by radioimmunoassay. When atropine sulphate 1 mg was given i.v. there was a rapid initial removal of the drug from the circulation in the first 10 min; thereafter the plasma concentration decreased more slowly. Atropine i.m. was rapidly absorbed with peak concentrations occurring at 30 min following injection. The plasma atropine concentration then decreased slowly, probably because of uptake of atropine by muscarinic cholinergic receptors. The chronotropic effect of atropine appeared to correspond to the concentration in plasma following i.m. administration. We conclude that i.m. atropine, as a premedication, should be given not later than 30 min before induction of anaesthesia.

Atropine is widely used as a premedicant for the reduction of secretions, protection against vagal overactivity and prevention of vomiting after operation (Kessel, 1974; Mirakhur et al., 1978). It is of interest to compare the therapeutic effect of the drug with its blood concentration. However, it has not been possible to determine the small concentrations of atropine found in plasma following typical doses, because of the lack of a sensitive method. Earlier investigations were performed with radio-labelled atropine. An obvious limitation of these studies was that the radioactivity rather than the parent compound was measured. Kalser and McLain (1970) administered ^{14}C-labelled atropine i.m. to adult volunteers and found that the concentration of carbon-14 in the blood reached maximum concentration after 15–30 min. Beerman, Hellström and Rosén (1971) reported that, after i.v. administration of ^{3}H-labelled atropine to humans, the plasma concentrations of radioactivity decreased rapidly. Oral administration on the other hand, resulted in maximum radioactivity in plasma after 1 h.

Recently, sensitive radioimmunoassay procedures for the determination of atropine have been reported (Fasth, Sollenberg and Sörbo, 1975; Wurzburger et al., 1977). They have only been used for determinations of atropine in experimental animals.

In the present investigation we determined the plasma concentrations of atropine following a single-dose i.v. or i.m. administration of the drug as premedication to surgical patients. An improved version of the radioimmunoassay developed by Fasth, Sollenberg and Sörbo (1975) was used.

METHODS

Patients, atropine administration and anaesthesia

The patients (ages 16–73 yr) underwent elective operations of comparable severity and duration (cholecystectomy, proximal vagotomy, mastectomy, internal fixation of tibial fracture, hemicolectomy). Single doses of atropine sulphate 1 mg were given as premedication to (a) six male patients i.v. immediately before induction of anaesthesia and (b) i.m. 30 min before the start of anaesthesia to two male and two female patients. The method of anaesthesia was the same for all patients: sodium thiopentone for induction followed by suxamethonium to permit intubation of the trachea. Fentanyl with 70% nitrous oxide in oxygen was given to maintain anaesthesia. When required, muscle relaxation was achieved with pancuronium.

Heparinized blood samples were taken immediately before atropine administration and then at intervals (figs 2, 3). Plasma was separated by centrifugation and stored frozen until analysed.

L. BERGHEM, PH.D.; U. BERGMAN, B.S.; Department of Biomedicine, National Defence Research Institute, Sundbyberg, Sweden. B. SCHILDT, M.D., Department of Anaesthesiology, Linköping University; B. SÖRBO, M.D., Department of Clinical Chemistry, Linköping University, Linköping, Sweden.

Correspondence to: Dr L. Berghem, ABC Research Department (FOA 4), National Defence Research Institute, S-901 82 Umeå, Sweden.

0007-0912/80/060597-05 $01.00

© Macmillan Journals Ltd 1980

Production of antiserum

The preparation of the immunogen (containing 21 residues of atropine per molecule of bovine serum albumin) has been described previously (Fasth, Sollenberg and Sörbo, 1975). Five male inbred chinchilla rabbits were immunized with immunogen 0.1 mg intradermally (Vaitukaitis et al., 1971). Blood samples were collected from the marginal ear vein 3 weeks after immunization and then at 1-week intervals. Serum was separated by centrifugation and assayed for anti-atropine antibodies (Fasth, Sollenberg and Sörbo, 1975). All animals responded with antibody production, which reached an optimum at 4–5 weeks after immunization. The concentration decreased slowly in four of the animals but in one it remained constant for 3 months. The antiserum used for the radioimmunoassay was harvested from the animals 9 weeks after the immunization.

Radioimmunoassay

A 2-ml aliquot of human plasma was mixed with 1 ml of sodium carbonate buffer 0.5 mol litre^{-1} (pH 10.8) in an acid-washed test tube and extracted with 10 ml of benzene-1.5% isoamyl alcohol. The benzene phase was separated by centrifugation and atropine re-extracted into 0.5 ml of hydrochloric acid 1 mol litre^{-1}. The latter was evaporated to dryness under vacuum over-night. To the residue was added 0.2 ml of sodium phosphate buffer 0.12 mol litre^{-1}, pH 7.5, horse control serum 0.2 ml (Seronorm, Nyegaard & Co., Oslo, Norway) and ^{3}H-atropine 10 μlitre containing atropine 20 pmol of specific activity 439 Ci mol^{-1} (The Radiochemical Centre, Amersham). After thorough mixing, 0.1 ml of anti-atropine antiserum, diluted 1 : 20 with saline, was added. The sample was incubated at 25 °C for 60 min and saturated ammonium sulphate 0.5 ml was added. The precipitate was centrifuged 30 min later, washed twice on the centrifuge with 50% saturated ammonium sulphate 1 ml and dissolved in distilled water 1.5 ml. This solution was transferred to a counting vial containing 15 ml of a Triton X-100–toluene based scintillation liquid (Patterson and Greene, 1965) and the sample was counted in a liquid scintillation counter. The amount of atropine present in the serum samples was obtained from a standard curve, prepared by adding known amounts of atropine to human control serum (Hyland Division, Travenol Laboratories, Lessines, Belgium). Linearization of the standard curve was obtained by plotting the quotient of the radioactivity bound in the absence (B_0) and in the presence (B) of unlabelled atropine *v.* the amount of the latter (fig. 1). The precision of the assay was evaluated by 19 repeated determinations of B_0/B for serum containing atropine 1.5 ng ml^{-1}. The result obtained was 1.24 ± 0.055 (mean ± SD). The sensitivity of the method, defined as the amount of atropine giving a B_0/B quotient significantly greater than 1.00, was 0.9 ng in the assay, corresponding to an atropine concentration in plasma of 0.5 ng ml^{-1}.

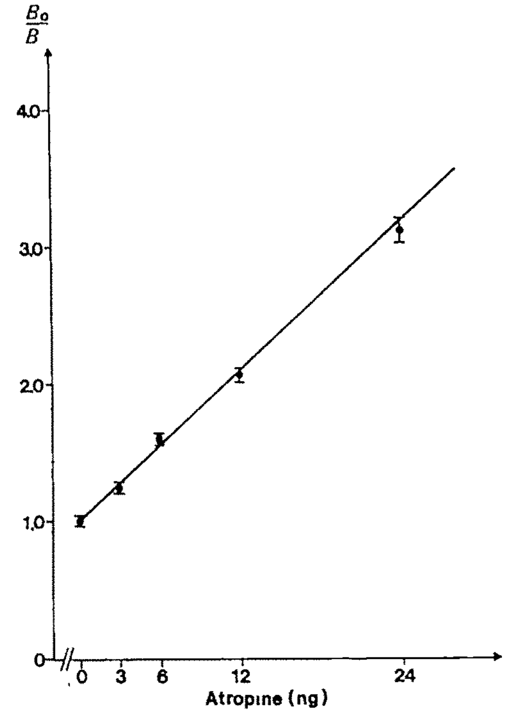


FIG. 1. Standard curves for atropine radioimmunoassay. The values presented are means ± SEM of 19 separately determined standard curves. The quotient of the radioactivity bound in the absence (B_0) and in the presence (B) of unlabelled atropine *v.* the serum concentration of the latter is indicated. B_0 was 42.7 ± 1.19% (mean ± SEM) of the total radioactivity present in the assay.

RESULTS

Atropine in plasma

Following an injection of atropine i.v. there was a rapid reduction of plasma concentrations within the first 10 min (fig. 2). It was calculated that the amount of atropine remaining in the circulation at 10 min after injection corresponded to less than 5% of the dose administered. Plasma concentrations then decreased more slowly during the following 50 min.

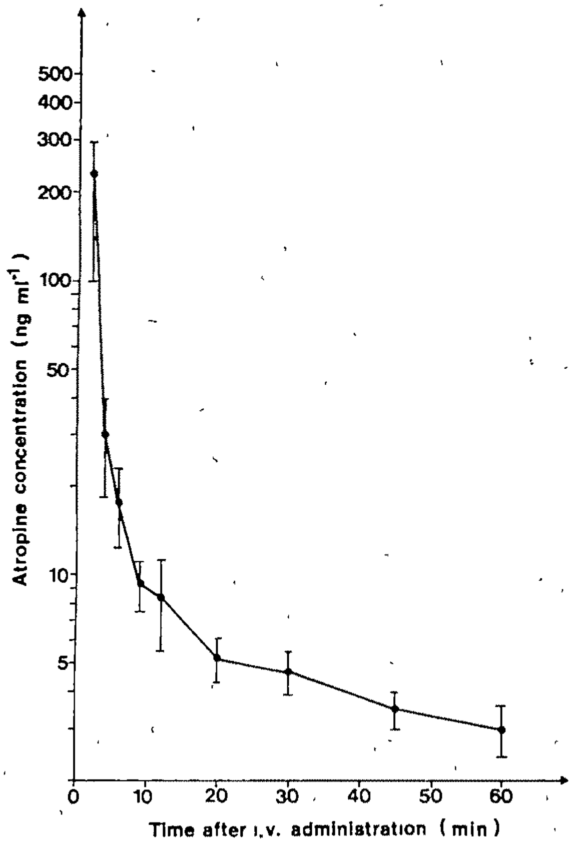


FIG. 2. Serum atropine concentrations after atropine sulphate 1 mg i.v. Each value represents the mean ± SEM of the determinations in six male patients.

One hour after i.v. administration, the plasma concentration was approximately the same as after i.m.

I.m. atropine was rapidly absorbed, reaching peak concentrations in plasma at 30 min (fig. 3). Plasma concentrations then decreased slowly, but were still detectable at 240 min after injection. The concentration after 1 h corresponded to that after i.v. administration.

Radioimmunoassay

The antiserum used was raised by intradermal immunization and was of a slightly greater potency than that obtained earlier after subcutaneous administration of the antigen (Fasth, Sollenberg and Sörbo, 1975). It thus bound 40% of the labelled atropine at a final dilution of 1 : 100, whereas the same effect was obtained with the earlier antiserum at 1 : 40 final dilution under otherwise identical conditions. Furthermore, the present antiserum recognized (+)-hyoscyamine and (−)-hyoscyamine (the two isomers of atropine) with equal efficiency, whereas the antiserum studied previously was less effective with (−)-hyoscyamine. We also verified that the drugs used for anaesthesia (sodium thiopentone, suxamethonium, fentanyl and pancuronium) were not recognized by the antiserum. In order to increase the sensitivity of the assay a concentration step, based on solvent extraction, was included. Various solvents were explored for this purpose and benzene, containing a small amount of isoamyl alcohol, gave the best results. The addition of isoamyl alcohol to non-polar solvents for extraction of basic drugs was originally

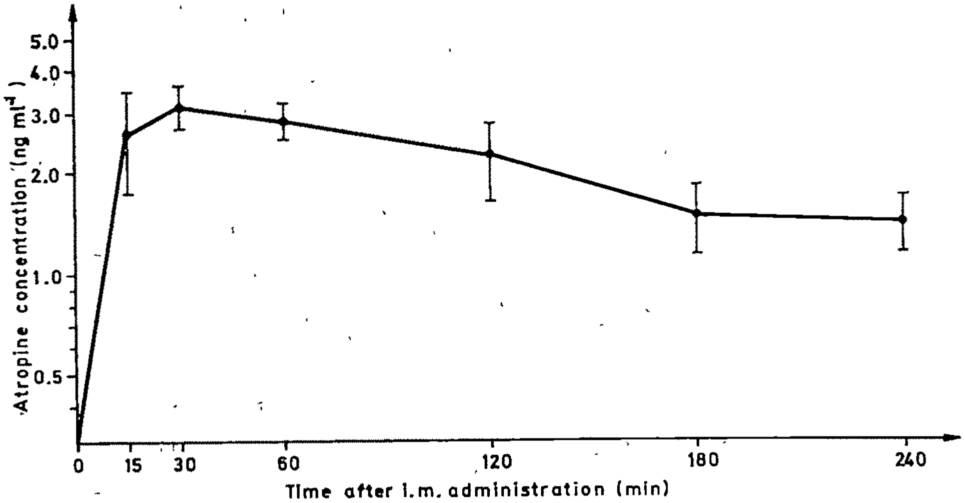


FIG. 3. Serum atropine concentration after atropine sulphate 1 mg i.m. Each value represents the mean ± SEM of the determinations in four patients (two males and two females).

suggested by Brodie, Udenfriend and Baer (1947) to prevent adsorption of the drug to glass surfaces. The yield of atropine in the concentration step was 84% but was corrected since both the standard and unknown plasma samples were taken through the same procedure.

DISCUSSION

A rapid initial removal of atropine from the circulation following injection i.v. was observed in the present investigation, confirming the findings of Beerman, Hellström and Rosén (1971) using ^{3}H-labelled atropine. However, these authors reported that the initial decrease was followed by a transient increase at 45 min, which was not observed by us. Wurzburger and others (1977), also using radioimmunoassay, observed a rapid decrease of blood concentrations of atropine in the dog after i.v. injection. This is probably a result of tissue uptake by muscarinic cholinergic receptors, as demonstrated in animals using radio-labelled atropine (Albanus et al., 1968). Atropine is a mixture of two isomers, (+)- and (−)-hyoscyamine, and only the latter is pharmacologically active. We found that less than 5% of the administered dose of atropine was present in the circulation 10 min after i.v. administration. As our radioimmunoassay detects both (+)- and (−)-hyoscyamine with equal efficiency, this indicates that the pharmacologically inactive (+)-isomer also disappears from the circulation by tissue uptake. This interpretation is supported by a recent report (Aronstam, Abood and MacNeill, 1977) indicating that certain muscarinic cholinergic receptors bind anticholinergic drugs without stereo-selectivity.

When atropine was administered by i.m. injection, the drug was rapidly absorbed with peak concentrations in plasma at 30 min. The plasma concentrations obtained at that time after i.m. injection were comparable to those found after i.v. administration. The clinical efficiency of the i.m. route for atropine is thus understandable. If the plasma concentration curve obtained after i.m. administration (fig. 3) is compared with the time course of the cardiac-accelerating effect of the drug (Sidell, Magness and Bollen, 1970), the heart rate closely follows the pattern set by the plasma concentrations. On the other hand, the depression of salivation is apparently a more delayed effect of atropine, reaching its peak effect about 100 min after i.m. administration (Murrin, 1973). This illustrates the well known fact that plasma concentrations of a drug may not always run parallel to its pharmacological effects.

A recent survey carried out in Great Britain and Ireland (Mirakhur et al., 1978) showed that atropine was the most popular anticholinergic premedicant. The principal mode of administration is i.m. and the i.v. route is second. The results of the present investigation indicate that, when atropine is given as premedication by i.m. injection, this should be performed at least 30 min before the start of anaesthesia.

REFERENCES

Albanus, L., Hammarström, L., Sundwall, A., Ullberg, S., and Vangbo, B. (1968). Distribution and metabolism of H^3-atropine in mice. *Acta Physiol. Scand.*, **73**, 447.

Aronstam, R. S., Abood, L. G., and MacNeill, M. K. (1977). Muscarinic cholinergic binding in human erythrocyte membranes. *Life Sci.*, **20**, 1175.

Beerman, B., Hellstrom, K., and Rosén, A. (1971). The gastrointestinal absorption of atropine in man. *Clin. Sci.*, **40**, 95.

Brodie, B. B., Udenfriend, S., and Baer, J. E. (1947). The estimation of basic organic compounds in biological material. I. General principles. *J. Biol. Chem.*, **168**, 299.

Fasth, A., Sollenberg, J., and Sorbo, B. (1975). Production and characterization of antibodies to atropine. *Acta Pharm. Suec.*, **12**, 311.

Kalser, S. C., and McLain, P. L. (1970). Atropine metabolism in man. *Clin. Pharmacol. Ther.*, **11**, 214.

Kessel, J. (1974). Atropine premedication. *Anaesth. Intens. Care*, **2**, 77.

Mirakhur, R. K., Clarke, R. S. J., Dundee, J. W., and McDonald, J. R. (1978). Anticholinergic drugs in anaesthesia. A survey of their present position. *Anaesthesia*, **33**, 133.

Murrin, K. R. (1973). A study of oral atropine in healthy adult subjects. *Br J. Anaesth.*, **45**, 475.

Patterson, M. S., and Greene, R. C. (1965). Measurement of low energy beta-emitters in aqueous solution by liquid scintillation counting of emulsions. *Anal. Chem.*, **37**, 854.

Sidell, F. R., Magness, J. S., and Bollen, T. E. (1970). Modification of the effects of atropine on human heart rate by pralidoxine. *Clin. Pharmacol. Ther.*, **11**, 68.

Vaitukaitis, J., Robbins, J. B., Nieschlag, E., and Ross, G. T. (1971). A method for producing specific antisera with small doses of immunogen. *J. Clin Endocrinol.*, **33**, 988.

Wurzburger, R. J., Miller, R. L., Boxenbaum, H. G., and Spector, S. (1977). Radioimmunoassay of atropine in plasma. *J. Pharmacol. Exp. Ther.*, **203**, 435.

DETERMINATION DES CONCENTRATIONS D'ATROPINE DANS LE PLASMA PAR RADIOIMMUNOESSAI APRES ADMINISTRATION D'UNE SEULE DOSE D'ATROPINE PAR VOIE INTRAVEINEUSE ET PAR VOIE INTRAMUSCULAIRE

RESUME

Les concentrations d'atropine dans le plasma ont été déterminées par radioimmunoessai après l'administration par voie intraveineuse ou intramusculaire de ce médicament

à des opérés. Lorsqu'on a administré par voie intraveineuse du sulfate d'atropine à raison de 1 mg, on a constaté à l'origine un retrait rapide du médicament de la circulation au cours des 10 premières minutes; après quoi les concentrations dans le plasma ont baissé plus lentement. L'atropine administrée par voie intramusculaire a été rapidement absorbée, les concentrations de pointe se produisant 30 min après l'injection. Les concentrations d'atropine dans le plasma ont ensuite baissé lentement, probablement à cause de la fixation de l'atropine par les récepteurs cholinergiques muscariniques. L'effet chronotropique de l'atropine semble correspondre à la concentration dans le plasma après l'administration intramusculaire. Nous en concluons que l'atropine administrée par voie intraveineuse, en tant que prémédicament, doit être injectée au moins 30 min avant l'induction de l'anesthésie.

ATROPIN-PLASMAKONZENTRATIONEN, BESTIMMT DURCH RADIOIMMUNOTEST NACH INTRAVENÖSER UND INTRAMUSKULÄRER EINZELDOSIS

ZUSAMMENFASSUNG

Die Atropin-Plasmakonzentrationen nach intravenöser oder intramuskulärer Verabreichung bei chirurgischen Patienten wurden mittels Radioimmunotest bestimmt. Wenn Atropinsulfat 1 mg intravenös gegeben wurde, kam es in den ersten 10 min zu einer rapiden Ausscheidung der Droge aus dem Kreislauf; danach sanken die Plasmakonzentrationen langsamer ab. Intramuskulär gegebenes Atropin wurde rapide absorbiert, mit Spitzenkonzentrationen 30 min nach der Injektion. Dann sanken die Plasmakonzentrationen langsamer ab, wohl wegen der Aufnahme von Atropin durch die muscarinischen cholinergischen Rezeptoren. Der chronotrope Effekt von Atropin schien der Plasmakonzentration nach intramuskulärer Verabreichung zu entsprechen. Wir schliessen daraus, dass Atropin intramuskulär als Vorbehandlung nicht später als 30 min vor Anästhesieenleitung verabreicht werden soll.

CONCENTRACIONES DE ATROPINA EN EL PLASMA DETERMINADAS POR RADIOINMUNOPRUEBA DESPUES DE ADMINISTRACION DE UNA DOSIS UNICA I.V. E I.M.

SUMARIO

Se determinó por radioinmunoprueba las concentraciones de atropina en el plasma después de la administración i.v. o i.m. a pacientes sometidos a cirujía. Cuando se administró 1 mg de sulfato de atropina i.v., se produjo una remoción inicial rápida de la substancia en la circulación durante los primeros 10 min; después, la concentración en el plasma disminuyó más despacio. La atropina i.m. fue asimilada rápidamente con concentraciones máximas 30 min después de la inyección. Luego, la concentración de atropina en el plasma disminuyó despacio, probablemente por motivo de la captación de la atropina por los receptores colinérgicos muscarínicos. El efecto cronotrópico de la atropina pareció corresponder a la concentración en el plasma después de la administración i.m. Llegamos a la conclusión de que la atropina i.m., como premedicación, no debe administrarse sino a más tardar 30 min antes de la inducción de la anestesia.

Br. J. Anaesth. (1980), **52**, 603

PROLONGATION OF THIOPENTONE ANAESTHESIA BY PROBENECID

S. KAUKINEN, M. EEROLA, AND P. YLITALO

SUMMARY

In a double-blind study, probenecid 0.5 or 1.0 g or placebo was given to 86 patients undergoing uterine curettage or gynaecological laparotomy 3 h before operation. The duration of anaesthesia in patients anaesthetized with thiopentone 7 mg kg^{-1} and premedicated with pethidine and atropine, was prolonged by 65% by probenecid 0.5 g, and by 46% by probenecid 1.0 g, compared with control ($P < 0.05$). In the absence of pethidine premedication, probenecid 0.5 g prolonged anaesthesia by 26% ($P < 0.1$). In patients without pethidine premedication anaesthetized with only thiopentone 4 mg kg^{-1} but who had no surgical stimulus during anaesthesia, probenecid increased the duration of the anaesthesia by 109% ($P < 0.1$). In this group the frequency of sleeping was 100%, as compared with 80% in the placebo-treated patients. Probenecid did not modify the response to pain and had no effect on apnoea, arterial pressure or heart rate.

Probenecid acts by inhibiting the active transport of organic acids through the renal tubular epithelium, and at other sites such as the choroid plexus (Spector and Lorenzo, 1974). In addition it has been found to have a sedative effect in experimental animals (Ahtee, Sharman and Vogt, 1970; Lyness and Mycek, 1978).

Probenecid is widely used in clinical practice to inhibit elimination of penicillin from serum by preventing its active renal tubular secretion. It may be administered just before operation when penicillin is used prophylactically to prevent wound infection. An important long-term indication for probenecid is as a uricosuric agent for gout.

Probenecid has been found to prolong both thiopentone and ketamine anaesthesia in mice and rats (Ylitalo, Saarnivaara and Ahtee, 1976). In man, it suppresses REM-sleep in psychotic patients (Kupfer, Foster and Powers, 1972) but there are no other studies of its effects on the central nervous system in man. We have examined the influence of probenecid on thiopentone anaesthesia in man.

PATIENTS AND ANAESTHESIA

This study received the consent of the patients and of the ethics committee of the hospital.

Eighty-six female patients undergoing gynaecological laparotomy or therapeutic abortion were in good health except for their presenting complaint and were receiving no medication. Three hours before anaesthesia the patients received 1 or 2 tablets of probenecid orally (1 tablet = 0.5 g of Probecid, Astra Pharmaceuticals, Södertälje, Sweden) or placebo (0.5 g of lactose), in a double-blind manner. Before anaesthesia, the patients were asked whether the tablets had caused drowsiness or any other complaints. One hour before anaesthesia atropine 0.0075 mg kg^{-1} was administered i.m. to all subjects and pethidine 1 mg kg^{-1} to some of the patients i.m. The patients were divided into three groups (table I); the design of the trial is shown in figure 1.

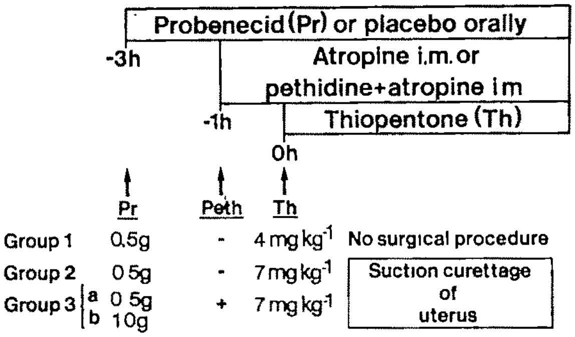


FIG. 1. Design of the study.

The patients in group 1 underwent gynaecological laparotomy. Anaesthesia was induced with thiopentone 4 mg kg^{-1} by injecting the dose i.v. over 30 s. The occurrence of loss of eyelid reflex and apnoea was noted. During sleep the patients were asked at 10-s intervals to open their eyes and the time at which they responded to this command was recorded. (Loss of eyelid reflex to this moment was recorded as the duration of anaesthesia.) Immediately

---

S. KAUKINEN, M.D.; M. EEROLA, M.D.; Department of Anaesthesiology, Tampere Central Hospital, Tampere, Finland. P. YLITALO, M.D., Department of Biomedical Sciences, University of Tampere, Tampere, Finland.

0007-0912/80/060603-05 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Characteristics (means ± SEM) of the different treatment groups undergoing gynaecological laparotomy or curettage of uterus and anaesthetized with thiopentone*

Group	n	Age (yr)	Weight (kg)
1 Premedication:			
atropine 0.0075 mg kg^{-1}			
Thiopentone 4 mg kg^{-1}			
No surgical procedure during thiopentone anaesthesia			
Probenecid 0.5 g	10	37 ± 2	68 ± 4
Placebo	10	33 ± 2	63 ± 4
2 Premedication:			
atropine 0.0075 mg kg^{-1}			
Thiopentone 7 mg kg^{-1}			
Surgical procedure: curettage of uterus			
Probenecid 0.5 g	11	25 ± 2	59 ± 2
Placebo	9	27 ± 2	61 ± 4
3 Premedication:			
atropine 0.0075 mg kg^{-1}			
pethidine 1 mg kg^{-1}			
Thiopentone 7 mg kg^{-1}			
Surgical procedure: curettage of uterus			
Probenecid			
(a) 0.5 g	9	27 ± 2	58 ± 2
(b) 1.0 g	15	30 ± 2	63 ± 3
Placebo	22	38 ± 1	62 ± 2

after the patient had opened her eyes she was re-anaesthetized for laparotomy with thiopentone and halothane, but only the duration of anaesthesia caused by the initial dose (4 mg kg^{-1}) of thiopentone was noted for the study.

In the remaining two groups the patients underwent therapeutic abortion by suction curettage under thiopentone anaesthesia. Immediately after the patient was asleep, suction curettage was performed. This procedure could be performed during anaesthesia induced by one dose of thiopentone 7 mg kg^{-1} because curettage lasted less than 3 min. The duration of anaesthesia was measured as in group 1. The tolerance of the patients to painful stimuli caused by curettage was registered as described in table III.

Arterial pressure was measured with an arm cuff and sphygmomanometer and heart rate by counting the radial pulse before the appropriate tablets were given just before atropine or atropine–pethidine premedication, just before the thiopentone injection and 1.5 min after the start of the injection of the anaesthetic.

After the patient had opened her eyes she was asked, at intervals of 10 s, her name and if she understood where she was. The time at which an unequivocal answer was given was noted (complete orientation). The time interval from opening the eyes to complete orientation was called the recovery time. Arterial pressure and heart rate were measured immediately after complete orientation.

The results are presented as mean ± SEM. Statistical significance of the differences between the means were evaluated with Student's t test, but if SD means differed significantly (compared with F-test), Mann–Whitney's U-test was used. When the nonparametric variables were tested χ^2-test was used.

RESULTS

Probenecid caused no obvious sedative or other psychic effect. In group 1, two of the 10 subjects treated with placebo did not fall asleep, but all 10 patients treated with probenecid did. In this group, where there was no pain stimulus during anaesthesia produced by thiopentone 4 mg kg^{-1}, the mean duration of anaesthesia was prolonged by 109% with probenecid, from 2.1 ± 0.3 min (mean ± SEM) to 4.4 ± 1.5 min ($P < 0.1$) (fig. 2). In the patients who did not receive pethidine premedication, who were anaesthetized with thiopentone 7 mg kg^{-1} and underwent suction curettage (group 2), probenecid 0.5 g lengthened the time of anaesthesia by 26%, from 3.0 ± 0.3 min to 3.8 ± 0.5 min ($P < 0.1$). The duration of anaesthesia, for curettage, induced with thiopentone 7 mg kg^{-1} in patients premedicated with pethidine was prolonged by 65% with probenecid 0.5 g (group 3a), from 6.3 ± 1.0 min to 10.4 ± 1.8 min ($P < 0.05$). Probenecid 1.0 g (group 3b) prolonged the time of anaesthesia by 46% to 9.2 ± 1.3 min ($P < 0.05$).

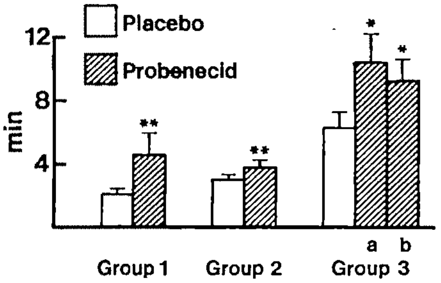


FIG. 2. Duration of thiopentone anaesthesia (min ± SEM) in patients treated with probenecid or placebo before operation and given atropine or atropine–pethidine for premedication. Treatments of different groups are given in table I. *$P < 0.05$, **$P < 0.1$ compared with placebo.

TABLE II. *Frequency of apnoea caused by thiopentone*

Group 1		Group 2		Group 3a and b		
					Probenecid	
Placebo	Probenecid 0.5 g	Placebo	Probenecid 0.5 g	Placebo	0.5 g	1.0 g
5/8 (63%)	6/10 (60%)	5/9 (56%)	4/11 (36%)	12/22 (59%)	5/9 (56%)	7/15 (47%)

TABLE III. *Motor responsiveness to the curettage of uterus under thiopentone anaesthesia. No = no motor responses; slight = slight twiches in extremities; moderate = movements in extremities and body but curettage performed without difficulty; strong = marked movement or patient wakened so that a supplementary dose of thiopentone had to be given*

	Group 2		Group 3a and b		
				Probenecid	
Motor responses	Placebo	Probenecid 0.5 g	Placebo	0.5 g	1.0 g
No	1/9 (11%)	2/11 (18%)	7/22 (32%)	4/9 (44%)	6/15 (40%)
Slight	2/9 (22%)	3/11 (27%)	7/22 (32%)	1/9 (11%)	6/15 (40%)
Moderate	4/9 (44%)	3/11 (27%)	5/22 (23%)	3/9 (33%)	0/15 (0%)
Strong	2/9 (22%)	3/11 (27%)	3/22 (14%)	1/9 (11%)	3/15 (20%)

Probenecid did not alter the frequency of apnoea in any group (table II). Neither did it change the response to curettage (table III). Recovery times were unaffected by probenecid as compared with those in patients who received the placebo ($P > 0.1$).

Arterial pressure and heart rate before, during, or after anaesthesia in the probenecid-treated patients did not differ from those in the placebo-treated subjects. The changes in arterial pressure and heart rate were small compared with the values before probenecid or placebo.

DISCUSSION

Probenecid pretreatment prolonged thiopentone anaesthesia by 46–65% on average in young females who had received atropine–pethidine premedication and underwent suction curettage of the uterus. The patients premedicated with atropine alone tolerated the curettage less well. For these patients, and for those who received a thiopentone dose (4 mg kg^{-1}) near to ED_{50} (3.5 mg kg^{-1}) (Tammisto et al., 1973) and had no painful stimulus during the anaesthesia, the prolongation of anaesthesia by probenecid was 26–109%. This prolongation was, however, less marked than in patients premedicated with pethidine also. The results agree with our previous findings in which probenecid prolonged thiopentone and ketamine anaesthesia in rats and mice (Ylitalo, Saarnivaara and Ahtee, 1976).

It might be supposed that the prolongation of sleeping time would be associated with deeper anaesthesia, but this was not seen; the frequency of apnoea, motor response to pain stimulus and changes in arterial pressure or heart rate were not influenced by probenecid. However, the pain stimulus (dilatation of the uterine cervix) was strong and was not constant, since some of the patients had delivered the products of conception while others had not. Thus our assessment of the depth of anaesthesia may not be accurate.

Because of its high perfusion rate, the brain quickly takes up the highly lipid-soluble thiopentone. Consequently, the patients fall asleep in the time in which thiopentone circulates from the arm to the brain (Ghoneim and Korttila, 1977). Probenecid inhibits the transport system for organic acids from cerebral tissue (Spector and Lorenzo, 1974). Also the transport of barbitone, a less lipid-soluble barbiturate than thiopentone, is thought to be inhibited by probenecid (Wahlström, 1978). Thiopentone is not known to have an active transport mechanism in the brain. The rapid recovery from anaesthesia is a result of the diffusion of the drug from the brain when the concentration in the blood decreases (Harvey, 1975; Ghoneim and Korttila, 1977). Thus the lengthening of anaesthesia by probenecid is not caused by inhibition of thiopentone outflow from brain. The metabolic destruction or elimination of thiopentone from the body is also of little importance in the time of wakening from anaesthesia.

Probenecid causes sedation in experimental animals (Ahtee, Sharman and Vogt, 1970; Lyness and Mycek, 1978) and suppresses REM-sleep in psychotic patients (Kupfer, Foster and Powers, 1972). Thus it may lessen the concentration of thiopentone needed for anaesthesia. As probenecid prevents the transport of organic acids from the brain, the pH in brain tissue may decrease. This would increase the un-ionized thiopentone fraction in the brain and promote the drug penetration to its site or sites of action. On the other hand, about 80% of thiopentone is bound to plasma proteins, and acidic drugs like acetylsalicylic acid and sulphonamides can displace it from binding sites (Harvey, 1975). Since between 80 and 95% of probenecid is also bound to plasma proteins (Brazeau, 1975), it may inhibit the binding of thiopentone to proteins. This would result in an increase of the free thiopentone fraction in plasma and allow more of the anaesthetic to enter brain.

Probenecid is widely used in the long-term treatment of gout and is also given in order to increase the duration of action of penicillin. In this study probenecid prolonged thiopentone anaesthesia by 26–109%. Prolongation of this degree is of practical significance in patients for whom thiopentone overdosage should be especially avoided.

REFERENCES

Ahtee, L., Sharman, D. F., and Vogt, M. (1970). Acid metabolites of monoamines in avian brain; effects of probenecid and reserpine. *Br. J. Pharmacol.*, **38**, 72.

Brazeau, P. (1975). Inhibitors of tubular transport of organic compounds. Probenecid; in *The Pharmacological Basis of Therapeutics*, 5th edn (eds L. S. Goodman and A. Gilman), p. 862. New York, Toronto, London: Macmillan.

Ghoneim, M. M., and Korttila, K. (1977). Pharmacokinetics of intravenous anaesthetics: implications for clinical use. *Clin. Pharmacokinet.*, **2**, 344.

Harvey, S. C. (1975). Hypnotics and sedatives. The barbiturates; in *The Pharmacological Basis of Therapeutics*, 5th edn (eds L. S. Goodman and A. Gilman), p. 102. New York, Toronto, London: Macmillan.

Kupfer, D. J., Foster, F. G., and Powers, M. (1972). Selective suppression of REM sleep by probenecid. *Brain Res.*, **41**, 210.

Lyness, W. H., and Mycek, M. J. (1978). The effect of probenecid on spontaneous motor activity in rats. *Neuropharmacology*, **17**, 211.

Spector, R., and Lorenzo, A. V. (1974). The effects of salicylate and probenecid on the cerebrospinal fluid transport of penicillin, aminosalicylic acid and iodide. *J. Pharmacol. Exp. Ther.*, **188**, 55.

Tammisto, T., Takki, S., Tigerstedt, I., and Kauste, A. (1973). A comparison of Althesin and thiopentone induction of anaesthesia. *Br. J. Anaesth.*, **45**, 100.

Wahlstrom, G. (1978). Increased penetration of barbital through the blood–brain barrier after pretreatment with probenecid. *Acta Pharmacol. Toxicol. (Copenh.)*, **43**, 260.

Ylitalo, P., Saarnivaara, L., and Ahtee, L. (1976). Effect of ketamine anaesthesia on the content of monoamines and their metabolites in the rat brain. *Acta Anaesthesiol. Scand.*, **20**, 216.

PROLONGATION DE L'ANESTHESIE AU THIOPENTONE A L'AIDE DE PROBENECIDE

RESUME

Au cours d'une étude à double inconnue, on a administré, 3 h avant l'opération, à 86 patientes devant subir un curetage utérin ou une laparotomie gynécologique, soit du probénécide (à raison de 0,5 ou de 1 g), soit un placebo. La durée de l'anesthésie des malades endormies au thiopentone (à raison de 7 mg kg^{-1}) et prétraitées à la péthidine et à l'atropine, a été prolongée de 65% avec 0,5 g de probénécide et de 46% avec 1 g de probénécide, par rapport au groupe témoin ($P < 0,05$). Lorsqu'il n'y a pas eu de prétraitement à la péthidine, le probénécide à raison de 0,5 g a prolongé l'anesthésie de 26% ($P < 0,1$). Sur les malades non prétraitées à la péthidine et seulement anesthésiées au thiopentone à raison de 4 mg kg^{-1}, mais n'ayant eu aucun stimulant chirurgical pendant l'anesthésie, le probénécide a prolongé la durée de l'anesthésie de 109% ($P < 0,1$). Dans ce groupe la fréquence de sommeil a été de 100%, alors qu'elle n'a été que de 80% chez les patientes traitées à l'aide d'un placebo. Le probénécide n'a pas modifié la réaction à la douleur et n'a eu aucun effet sur l'apnée, la pression artérielle ou la fréquence cardiaque.

VERLÄNGERUNG DER THIOPENTON-ANÄSTHESIE DURCH PROBENECID

ZUSAMMENFASSUNG

In einer Doppelblind-Studie wurde Probenecid 0,5 oder 1,0 oder aber ein Plazebo an 86 Patienten vor einer uterinen Curettage oder einer gynäkologische Laparotomie verabreicht (3 Stunden vorher). Die Anasthesiewirkung bei Patienten, die mit Thiopenton 7 mg kg^{-1} anästhesiert und mit Pethidin und Atropin vorbehandelt worden waren, wurde um 65% verlängert durch Probenecid 0,5 g, und um

46% durch 1,0 g, verglichen mit der Kontrollgruppe ($P < 0{,}05$). Ohne Pethidin-Vorbehandlung konnte durch Probenecid 0,5 g die Anästhesie um 26% ($P < 0{,}1$) verlängert werden. Bei Patienten ohne Pethidin-Vorbehandlung, und anästhesiert nur mit Thiopenton 4 mg kg^{-1}, aber ohne chirurgischen Stimulus während der Anästhesie konnte Probenecid die Anasthesiewirkung um 109% ($P < 0{,}1$) verlängern. Die Schlafhaufigkeit in dieser Gruppe war 100%, verglichen mit 80% bei den Plazebo-Patienten. Probenecid modifizierte die Reaktion auf Schmerzen nicht, und hatte keine Wirkung auf Apnoe, arteriellen Druck und Pulszahl.

PROLONGACION DE LA ANESTESIA POR TIOPENTONA POR MEDIO DEL PROBENECIDO

SUMARIO

En un estudio doble-ciego, se administró 0,5 ó 1,0 g de probenecido o de placebo a 86 pacientes sometidos a un raspado uterino o una laparotomía ginecológica 3 h antes de la operación. La duración de la anestesia en pacientes anestesiados por 7 mg kg^{-1} de tiopentona y con premedicación por petidina y atropina, fue prolongada en un 65% mediante 0,5 g de probenecido y en un 46% con 1,0 g de probenecido, en comparación con el control ($P < 0{,}05$). En la ausencia de premedicación por petidina, 0,5 g de probenecido prolongó la anestesia en un 26% ($P < 0{,}1$). En los pacientes que carecían de premedicación por petidina y anestesiados con solamente 4 mg kg^{-1} de tiopentona, pero que no recibieron ningún estimulante durante la anestesia, el probenecido aumentó la duración de la anestesia en un 109% ($P < 0{,}1$). En este grupo, la frecuencia del sueño fue de 100%, en comparación con un 80% en los pacientes tratados con placebo. El probenecido no alteró la respuesta al dolor y no tuvo ningún efecto sobre la apnea, la presión arterial o el ritmo cárdiaco.

Br. J. Anaesth. (1980), **52**, 609

LOCAL REACTIONS TO I.V. DIAZEPAM IN THREE DIFFERENT FORMULATIONS

A. SCHOU OLESEN AND M. S. HÜTTEL

SUMMARY

Local venous reactions during and after i.v. injections of three different formulations of diazepam were studied in 200 patients undergoing gastroscopy. Of the patients receiving diazepam in propylene glycol (Stesolid) 78% experienced pain on injection and 48% subsequently developed clinical evidence of thrombophlebitis. The figures for Stesolid MR (diazepam in Cremophor EL) were 38% and 9% respectively. A significant decrease was achieved (pain on injection 1%; clinical thrombophlebitis 4%) when using Diazemuls, a new formulation in which diazepam is dissolved in oil and emulsified in water. Since no difference in the therapeutic effect of the different formulations was observed, Diazemuls represents a clear advantage to Stesolid and Stesolid MR.

Diazepam dissolved in propylene glycol (Stesolid), causes a high frequency of pain (Siebke, Ellertsen and Lind, 1976) and venous thrombosis (Hegarty and Dundee, 1977) when injected i.v. Assuming that the solvent system may be responsible for these complications, attempts have been made to use macrogoli ricinoleas (Cremophor EL) as an alternative solvent (Stesolid MR). However, although the frequency of venous complications was decreased, the change to this preparation led to the appearance of severe adverse reactions (Schou Olesen and Hüttel, 1978).

Since diazepam is lipid-soluble, it is possible to dissolve the drug in oil, which can then be emulsified in water (Jeppsson and Ljungberg, 1975) without influencing the clinical effect of the drug (Thorn-Alquist, 1977).

On the basis of this principle Kabi–Vitrum, Sweden have produced a new formulation (Diazemuls —under registration in the U.K.) in which diazepam is dissolved in soybean oil and emulsified in water by means of acetylated monoglycerides and egg-yolk phosphatides. The same technique has been employed for Intralipid, the fat emulsion used for i.v. nutrition.

The aim of this investigation was to compare local venous reactions during and after the i.v. injection of these three preparations (diazepam in propylene glycol, diazepam in Cremophor EL and diazepam in oil) all of which have a diazepam concentration of 5 mg ml^{-1}.

PATIENTS AND METHODS

Two hundred consecutive adult patients admitted to the hospital for gastroscopy were studied. They were allocated randomly to the three groups. It was not possible to perform a true double-blind study because of the different appearances of the preparations, but as the authors did not administer the drug they were unaware of the formulation given.

A disposable Teflon cannula (Venflon no. 1.2 Viggo, Sweden) was used in all patients, placed in the left cephalic vein. Using an injection rate of 5 mg min^{-1}, sufficient medication was given to sedate the patient or until a maximum dose of 30mg was reached. No other drug was given through this cannula. After completion of the injection the cannula was withdrawn. If leakage outside the vein or haematoma occurred, if, by mistake, the vein was used subsequently for venepuncture, or if an i.v. infusion was given later in that arm, the patient was excluded from the study.

Symptoms of discomfort or pain arising from the injection, mentioned either spontaneously or on questioning, were recorded by the nurse in charge when the immediate local reactions were noted.

Each patient was seen by one of us no later than the following day and again daily until discharged. Mean observation time was 4 days (range 1–14 days). The site of injection was examined and the presence or absence of tenderness on palpation of the vein, venous thickening and local erythema were recorded. Two weeks after the injection patients received a questionnaire referring to the same points. Whenever the written answers left any doubt the patient was seen by one of us.

ANDERS SCHOU OLESEN, M.D.; MOGENS S. HÜTTEL, M.D.; Department of Anaesthetics and Intensive Care, Aalborg Hospital, DK-9100 Aalborg, Denmark.

Correspondence to M. S. H., Department of Anaesthesia, Odense Sygehus, DK-5000 Odense C, Denmark.

0007-0912/80/060609-03 $01.00

© Macmillan Journals Ltd 1980

Thrombophlebitis was diagnosed when at least two out of three symptoms were recorded.

For statistical evaluation Fisher's Exact Probability test was used.

RESULTS

Only three patients did not answer the questionnaire, bringing the numbers taking part to 197. The results are shown in table I.

TABLE I. *Local venous sequelae to i.v. injection of three formulations of diazepam. Results are numbers (and percentages) out of* 197 *patients*

Symptoms or signs	Diazemuls ($n = 67$)	Stesolid MR ($n = 66$)	Stesolid ($n = 64$)
Pain on injection			
Elicited spontaneously	0 (0)	9 (14)	28 (44)
After questioning	1 (1)	25 (38)	50 (78)
Local reactions			
Redness	4 (6)	3 (5)	20 (31)
Tenderness	4 (6)	6 (9)	29 (45)
Induration	2 (3)	5 (8)	24 (38)
All three symptoms	2 (3)	2 (3)	11 (17)
Thrombophlebitis	4 (6)	6 (9)	31 (48)
Without pain or local reactions	64 (96)	37 (49)	9 (14)

The groups were comparable with regard to age, sex and mean dose of diazepam, which in all groups was 21 mg (range 7–30 mg).

There were no apparent differences between the three formulations with respect to onset, duration or magnitude of the therapeutic effect.

DISCUSSION

In support of previous studies by Graham, Pagano and Conner (1978), who found a high frequency of painful injections with diazepam dissolved in an aqueous vehicle composed of organic solvents consisting mainly of propylene glycol, ethyl alcohol and sodium benzoate in benzoic acid (Valium), we found that 78% of patients receiving an undiluted aqueous diazepam preparation containing propylene glycol experienced pain on injection, regardless of dosage. This was decreased significantly when the other two preparations were used, and it was noteworthy that only one patient complained when Diazemuls was given (table I).

The frequency of thrombophlebitis was 48% when the aqueous solution of diazepam (Stesolid) was used. A follow-up of only 2–3 days will underestimate the frequency of venous sequelae, since thrombophlebitis may not appear until 10–14 days after the administration (Hegarty and Dundee, 1977). The present study was designed to counter this problem, and the intense follow-up may be the reason for the relatively high frequency of local reactions observed.

All differences were statistically significant ($P < 0.001$) except that comparing Diazemuls and Stesolid MR for thrombophlebitis. Diazemuls is, nevertheless, superior when combining pain on injection and thrombophlebitis.

The introduction of Stesolid MR with Cremophor EL as solvent caused a significant decrease in thrombophlebitis (Siebke, Ellertsen and Lind, 1976) but this led to severe anaphylactic reactions (Schou Olesen and Hüttel, 1978). We have found recently (Hüttel, Schou Olesen and Stoffersen, 1980) that some of these reactions may be a result of complement activation via the alternative pathway. Since the same phenomenon has been shown by Watkins and colleagues (1976) with Althesin, which also has Cremophor EL as solvent, it is probable that the solvent itself is responsible for the reactions.

Von Dardel, Mebius and Mossberg (1976), studying diazepam in an emulsion, found a significant decrease in the frequency of adverse local vascular reactions similar to that observed in the present investigation. Since then von Dardel and colleagues have used Diazemuls safely in more than 10 000 patients without anaphlyactic reaction (O. von Dardel, personal communication).

We conclude that a significant decrease in the frequency of local vascular side-effects can be achieved by using diazepam in the lipid emulsion form with no alteration in the therapeutic effect.

ACKNOWLEDGEMENTS

We extend our gratitude to the anaesthetic nursing staff, without whose able help this study could not have been completed.

Diazemuls was kindly supplied by Kabi–Vitrum A/S.

The investigation was supported in part by a grant from Aalborg Kommunes Fond for Medicinsk Forskning.

REFERENCES

von Dardel, O., Mebius, C., and Mossberg, T. (1976). Diazepam in emulsion form for intravenous usage. *Acta Anaesthesiol. Scand.*, **20**, 221.

Graham, C. W., Pagano, R. R., and Conner, J. T. (1978). Pain and clinical thrombophlebitis following intravenous diazepam and lorazepam. *Anaesthesia*, **33**, 188.

Hegarty, J. E., and Dundee, J. W. (1977). Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. *Br. Med. J.*, **2**, 1384.

Hüttel, M. S., Schou Olesen, A., and Stoffersen, E. (1980). Complement-mediated reactions to diazepam with Cremophor EL as solvent (Stesolid MR). *Br. J. Anaesth.*, **52**, 77.

Jeppsson, R., and Ljungberg, S. (1975). Anticonvulsant activity in mice of diazepam in an emulsion formulation for intravenous administration. *Acta Pharmacol. Toxicol.*, **36**, 312.

Schou Olesen, A., and Hüttel, M. S. (1978). Circulatory collapse following intravenous administration of Stesolid MR. *Ugeskr. Laeger.*, **140**, 2644.

Siebke, H., Ellertsen, B. B., and Lind, B. (1976). Reactions to intravenous injections of diazepam. *Br. J. Anaesth.*, **48**, 1187.

Thorn-Alquist, A. M. (1977). Parenteral use of diazepam in an emulsion formulation. A clinical study. *Acta Anaesthesiol. Scand.*, **21**, 400.

Watkins, J., Clark, A., Appleyard, T. N., and Padfield, A. (1976). Immune-mediated reactions to Althesin (alphaxalone). *Br. J. Anaesth.*, **48**, 881.

REACTIONS LOCALES A L'INJECTION INTRAVEINEUSE DE DIAZEPAM PREPARE SUIVANT TROIS DIFFERENTES FORMULES

RESUME

On a étudié sur 200 malades subissant une gastroscopie, les réactions veineuses locales pendant et après l'injection intraveineuse de trois différentes préparations de diazépam. Parmi les malades auxquels on a administré le diazépam dans du propylène glycol (Stesolid), 78% ont ressenti une douleur lors de l'injection, et 48% ont par la suite développé des signes cliniques de thrombophlébite. Les chiffres correspondants pour le Stesolid MR (diazépam dans crémophor EL) ont été respectivement de 38% et de 9%. On a obtenu une diminution importante de la douleur au moment de l'injection (1%) et des signes cliniques de thrombophlébite (4%), lorsqu'on a utilisé du Diazémuls, qui est une nouvelle formule dans laquelle le diazépam est dissout dans l'huile et émulsifié dans l'eau. Du fait que l'on n'a observé aucune différence dans les effets thérapeutiques des diverses préparations, le Diazémuls présente un net avantage par rapport au Stesolid et au Stesolid MR.

LOKALE REAKTIONEN AUF INTRAVENÖSE EINSPRITZUNG VON DIAZEPAM IN 3 VERSCHIEDENEN FORMULIERUNGEN

ZUSAMMENFASSUNG

Lokale venöse Reaktionen während und nach intravenöser Einspritzung von 3 verschiedenen Formulierungen von Diazepam wurden bei 200 Gastroskopie-Patienten studiert. Von den Patienten, die Diazepam in Form von Stesolid erhielten, erfuhren 78% Schmerzen bei der Einspritzung, und bei 48% zeigte sich spater ein klinischer Befund von Thrombophlebitis. Die entsprechenden Zahlen fur Stesolid MR waren 38% und 9%. Eine bedeutende Reduzierung (Schmerzen bei der Einspritzung bei 1%; klinischer Befund von Thrombophlebitis bei 4%) wurde mit Diazemuls erreicht, eine neue Formulierung, in der Diazepam in Öl aufgelöst und in Wasser emulgiert wird. Da in Bezug auf die therapeutische Wirkung kein Unterschied zwischen den verschiedenen Formulierungen festgestellt werden konnte, bietet Diazemuls klare Vorteile gegenüber Stesolid und Stesolid MR.

REACCIONES LOCALES AL DIAZEPAM I.V. EN TRES FORMULAS DISTINTAS

SUMARIO

Se estudiaron las reacciones venosas locales durante y después de inyecciones i.v. de tres fórmulas distintas de diazepam en 200 pacientes sometidos a gastroscopia. De los pacientes que recibieron diazepam en glicol de propileno (Stesolid), un 78% padeció de dolores al momento de la inyección y un 48% demostró consiguientemente prueba clínica de tromboflebitis. Las cifras relativas al MR Stesolid (diazepam en cremofor EL) fueron de 38% y 9%, respectivamente. Se obtuvo una disminución significativa (dolor al momento de la inyección 1%; tromboflebitis clínica 4%) al usar el Diazemuls, una nueva fórmula en la cual se disuelve al diazepam en aceite y se emulsifica en agua. Puesto que no se observó ninguna diferencia en los efectos terapeúticos de las distintas fórmulas, el Diazemuls brinda una clara ventaja sobre Stesolid y Stesolid MR.

Br. J. Anaesth. (1980), **52**, 613

COMPARISON OF I.M. LYSINE ACETYLSALICYLATE AND OXYCODONE IN THE TREATMENT OF PAIN AFTER OPERATION

K. KORTTILA, O. M. PENTTI AND J. AUVINEN

SUMMARY

Lysine acetylsalicylate (LAS) is a soluble salt of acetylsalicylic acid and can be given parenterally. LAS 12.5 mg kg^{-1} and 25 mg kg^{-1} were compared with oxycodone 0.15 mg kg^{-1} in the treatment of pain after operation in 60 patients undergoing varicose vein surgery. Both treatments almost completely relieved moderate to severe pain for the 3-h observation period. The time until the peak of action was longer after LAS (60–90 min) than after oxycodone (30–60 min). No significant differences were found between the smaller and larger doses of LAS, suggesting a plateau effect. Further clinical experiments with LAS using i.v. mode of administration and other pain models are warranted.

Advantages of antipyretic analgesics over narcotic analgesics in treatment of pain after operation include absence of depression of breathing (Woodbury and Fingl, 1975), and less harmful effects on psychomotor performance, which is important in outpatient practice (Korttila, 1976).

Since the absorption of orally administered drugs is often unpredicatable immediately after anaesthesia, the use of antipyretic analgesics in treatment of pain after operation has been limited. Lysine acetylsalicylate is a soluble salt of acetylsalicylic acid and can be given parenterally. It has been reported to have less influence on haemostasis and to produce less intestinal microbleeding than comparable doses of acetylsalicylic acid (Aron, Delbarre and Besnard, 1975; Schöndorf, 1975).

Previous investigators have suggested that the efficacy of lysine acetylsalicylate (LAS) is comparable to that of narcotic analgesics. Kweekel-DeVries and others (1974) compared LAS 1.8 g administered i.m. with morphine 10 mg in treatment of pain after gynaecological laparotomy and found a similar degree of relief of pain. Cattaneo, Rivara and Launo (1975) gave LAS i.v. and pethidine i.m. to patients suffering pain after cholecystectomy and came to the conclusion that LAS 14.67 mg kg^{-1} given i.v. corresponds to pethidine 1 mg kg^{-1} given i.m. Papatheodossiou (1976) concluded that parenterally administered LAS was comparable to pentazocine when given for pain relief after orthopaedic and gynaecological operations.

This previous work prompted us to undertake a double-blind controlled comparison of LAS and oxycodone in the treatment of pain after operation.

MATERIALS AND METHODS

Patients and anaesthesia

We studied 60 patients undergoing varicose vein surgery (table I). All of the patients were ASA Class I–II in respect of their general health and informed consent was obtained from each one. Premedication was diazepam 7.5, 10 or 12.5 mg orally according to weight 60–90 min and atropine 0.01 mg kg^{-1} i.v. 5 min before induction of anaesthesia. Anaesthesia was induced with a sleep-dose (approximately 7 mg kg^{-1}) of propanidid and maintained with 1–2% halothane in 66% nitrous oxide in oxygen. Tracheal intubation was facilitated by suxamethonium 1.0 mg kg^{-1} i.v., but no other drug was given during anaesthesia. The average duration of anaesthesia was 60–90 min (table I).

Administration of analgesics

At an average of 60–90 min after operation patients complained of moderate to severe pain. Then they received, in double-blind random fashion from coded ampoules, lysine acetylsalicylate (ONR-297, Orion, Helsinki) (LAS) 12.5 mg kg^{-1} or 25 mg kg^{-1} or oxycodone chloride (Oxanest, Leiras, Turku) 0.15 mg kg^{-1} i.m. into the lateral vastus muscle of thigh.

K. KORTTILA,* M.D., Department of Anaesthesia, Helsinki University Central Hospital, Helsinki, Finland. O. M. PENTTI, M.D., Department of Anaesthesia, Middle Finland Central Hospital, Jyväskyla, Finland. J. AUVINEN, M.PHARM., Orion Pharmaceutical Company, Helsinki, Finland.

* Present address (for reprint requests): Department of Anesthesia, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242, U.S.A.

0007–0912/80/060613–05 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Characteristics of test groups and injected drug doses (means ± SD)*

Treatment	Number of patients (male/female)	Age (yr)	Weight (kg)	Height (cm)	Duration of anaesthesia (min)
Oxycodone 0.15 mg kg^{-1}	13 (2/11)	47±10	69±9	166±4	67±22
LAS 12.5 mg kg^{-1}	22 (2/20)	46±10	72±12	165±7	63±16
LAS 25 mg kg^{-1}	25 (1/24)	45±10	65±10	163±7	73±22

LAS was prepared by dissolving equivalent amounts of acetylsalicylic acid and lysine plus approximately 10% of glycine (aminoacetic acid) into water followed by lyophilization into vials as lysine acetylsalicylate powder. Before injection, 7 ml of sterile water was used as solvent to obtain solutions containing LAS 150 or 300 mg ml^{-1} with the pH value of 5.5.

Assessment of analgesic efficacy and side-effects

Trained nurses asked the patients to score the intensity of pain and the pain relief before and at 15, 30, 45, 60, 90, 120, 150 and 180 min after administration of LAS or oxycodone as 0 = nil, 1 = slight, 2 = moderate, and 3 = severe pain or complete pain relief. Six patients given LAS 25 mg kg^{-1}, one given LAS 12.5 mg kg^{-1} and one given oxycodone were given oxycodone 0.15 mg kg^{-1} 90–120 min after anaesthesia in addition to the test dose because of persistent severe pain. In these patients pain was considered to be severe (3) and pain relief none (0) for each assessment after the additional dose of oxycodone as a known analgesic had been given.

Heart rate was counted from the e.c.g., systolic arterial pressure was measured by auscultation and sphygmomanometry and respiratory rate was noted. Other side-effects, especially drowsiness, nausea, vomiting, sweating and headache were rated by the nurses as 0 = nil, 1 = slight, 2 = moderate, and 3 = severe.

Statistics

Changes in heart rate, arterial pressure and respiratory rate were compared with Student's *t* test. Pain intensity, pain relief, and the frequency of side-effects were compared with Chi-square test and Fisher exact probability test because of the non-parametric nature of these data.

RESULTS

Pain intensity and pain relief

After oxycodone moderate to severe pain was alleviated to almost nil and pain relief was almost

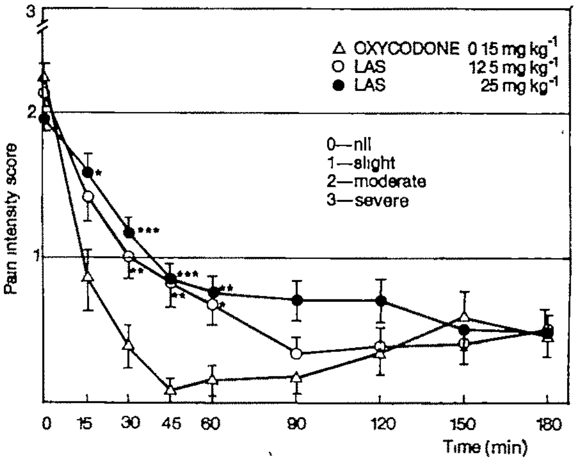


FIG. 1. Pain intensity as a function of time in different test groups (mean ± SEM). *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ in comparison with oxycodone.

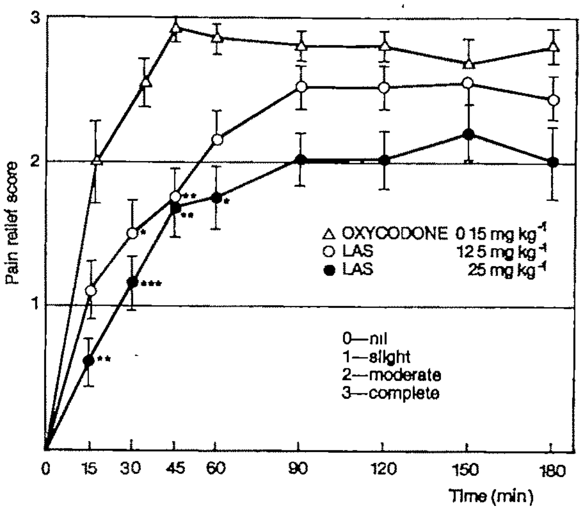


FIG. 2. Pain relief as a function of time in different test groups (mean ± SEM). *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ in comparison with oxycodone.

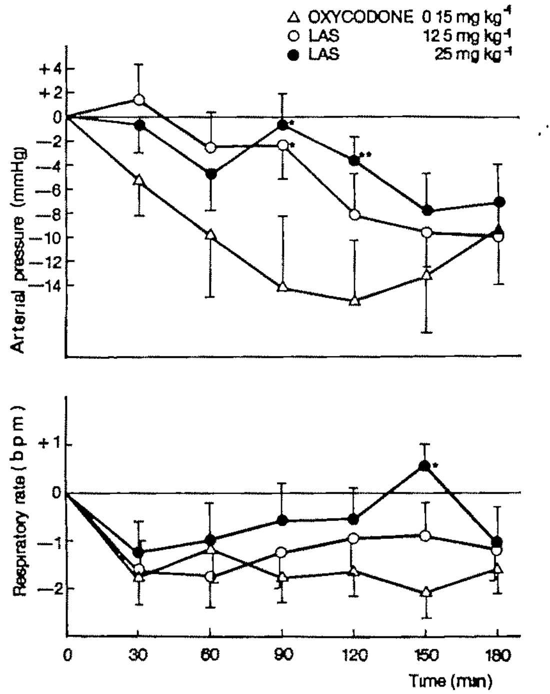


FIG. 3. Changes in systolic arterial pressure and respiratory rate as a function of time in different test groups (mean ± SEM). $^*P<0.05$ and $^{**}P<0.01$ in comparison with oxycodone.

complete within 30 min. Its duration of action lasted for the whole observation period of (3 h) (figs 1, 2). Both doses of LAS also alleviated pain, but its speed of action was significantly ($P<0.05$ to $P<0.001$) slower than that of oxycodone. Pain intensity was greater and pain relief worse 30–60 min after both doses of LAS when compared with the scores after oxycodone, but no significant differences were noticed between the three treatments in either of these indices 90–180 min after drug administration (figs 1, 2).

No significant differences were noticed in the action of LAS 12.5 mg kg^{-1} or 25 mg kg^{-1}. However, pain relief was worse after the greater dose of LAS than after the smaller one (figs 1, 2).

Side-effects

No clinically significant changes were noticed in arterial pressure, heart rate or respiratory rate. Heart rate remained almost unaltered after each treatment. Systolic arterial pressure averaged 120 mm Hg before the injection of analgesics and decreased by an average of 15 mm Hg after oxycodone but less after both doses of LAS (fig. 3). The respiratory rate of 20 b.p.m. was not decreased by more than a mean of 2 b.p.m. after each of the three treatments (fig. 3).

Headache, emetic symptoms and tiredness were the most common side-effects, but no significant differences were noticed in the frequency among the three groups (table II).

TABLE II. *Side-effects (number of patients) after i.m. injection of oxycodone chloride or lysine acetylsalicylate (LAS), for pain relief after operation. No significant differences between groups (Chi-square and Fisher exact probability test)*

	Treatment		
Side-effect	Oxycodone 0.15 mg kg^{-1} ($n=13$)	LAS 25 mg kg^{-1} ($n=25$)	LAS 12.5 mg kg^{-1} ($n=22$)
Tiredness	3	7	10
slight	2	7	9
moderate	1	0	1
severe	0	0	0
Nausea	4	11	5
slight	2	6	0
moderate	2	2	3
severe	0	3	2
Vomiting	3	7	4
slight	0	1	0
moderate	2	5	2
severe	1	1	2
Sweating	2	3	0
slight	1	3	0
moderate	1	0	0
severe	0	0	0
Headache	4	16	12
slight	3	13	8
moderate	1	3	3
severe	0	0	1
Others	0		
vertigo		1	
tremor			1

DISCUSSION

The principal result was that LAS relieved pain almost as effectively as oxycodone, but the speed of action of LAS was distinctly slower than that of oxycodone. No significant differences were noted between the effects of the smaller and larger doses of LAS.

Trial design

A comparison of the analgesic efficacy of the drugs studied is justified in this investigation, since type and duration of anaesthesia and type of operation were similar in each group. The groups differed only in respect of the analgesics given. The doses of LAS were based on reports in the literature (Kweekel DeVries et al., 1974; Ventafridda and Spreavice, 1974; Cattaneo, Rivara and Launo, 1975; Papatheodossiou, 1976) on the analgesic efficacy of LAS in the treatment of pain. The dose of oxycodone used corresponds to the same dose (0.15 mg kg^{-1}) of morphine and both are generally known to have a good analgesic action (Jaffe and Martin, 1975).

A placebo was not included for ethical reasons because our previous clinical experience indicated that, after operations of the type undertaken in this study, moderate to severe pain lasts more than 3 h if not treated. The relief of pain after the analgesics were given can be considered to be a result of the drugs, and not of the spontaneous alleviation of the pain.

The type of anaesthesia used provides very rapid recovery and minimal residual effects (Korttila and Linnoila, 1975; Korttila et al., 1975; Korttila et al., 1977). The results of the present study best relate to treatment of moderate somatic pain in alert patients. Clinical situations which differ from this study, such as laparotomy or bone surgery, would have to be assessed separately.

Effects of lysine acetylsalicylate

The slow onset of action of lysine acetylsalicylate is consistent with its pharmacokinetics (Ventafridda and Martino, 1976). LAS is first converted to acetylsalicylic acid which is metabolized in the liver to salicylic acid, the active drug. The analgesic effect seems to occur after i.v. injection of LAS during high plasma concentrations of salicylic acid when the hydrolysis of acetylsalicylic acid has already occurred (Ventafridda and Martino, 1976). Even following i.v. injection of LAS, the maximum effect was not reached until 60 min after injection when enough salicylic acid had been produced (Ventafridda and Martino, 1976).

The finding that doubling the dose of LAS did not improve its analgesic efficacy, that is a plateau effect occurred, has not been suggested before for LAS. The greater dose was actually less efficient than the smaller dose. Recently, a paradoxical effect of aspirin on bleeding-time has been reported; small doses prolong the bleeding time but not larger doses (O'Grady and Moncada, 1978; Rajah, Penny and Kester, 1978). This has been explained by the different actions of small and large doses of acetylsalicylic acid on cyclo-oxygenase, the enzyme involved in the synthesis of one of the prostaglandins (P.G.I$_2$) required in the blood clotting process (O'Grady and Moncada, 1978).

The mechanism of analgesic action of acetylsalicylic acid is also related to prostaglandin synthesis. Salicylic acid is believed to decrease the sensitivity of pain receptors to nociceptic stimuli by decreasing prostaglandin synthesis (Collier, 1971; Vane, 1971). If inhibition of the synthesis of prostaglandins related to mediating painful stimuli, like that of those involved in blood clotting, is dependent on the dose of acetylsalicylic acid, greater doses of LAS need not be as effective as smaller doses in pain relief.

Our results suggest that i.m. LAS is effective in treatment of moderate to severe somatic pain. Further clinical experiments with lysine acetylsalicylate using i.v. administration and other pain models are warranted.

ACKNOWLEDGEMENT

The authors thank personnel of Middle Finland Central Hospital for their co-operation during the study.

REFERENCES

Aron, E., Delbarre, B., and Besnard, J. C. (1975). Prévention des accidents digestifs provoqués par l'aspirine. *Med. Chir. Dig.*, **4**, 61.

Cattaneo, A. D., Rivara, A., and Launo, C. (1975). Clinical evaluation of lysine acetylsalicylate in the treatment of postoperative pain. *Min. Anest.*, **41**, 599.

Collier, H. O. J. (1971). Prostaglandins and aspirin. *Nature (Lond.)* **232**, 17.

Jaffe, J. H., and Martin, W. R. (1975). Narcotic analgesics and antagonists; in *Pharmacological Basis of Therapeutics* (eds L. S. Goodman and A. Gilman), p. 245. New York: Macmillan Publishing Co., Inc.

Korttila, K. (1976). Minor outpatient anaesthesia and driving. *Mod. Probl. Pharmacopsych.*, **11–13**, 91.

—— Linnoila, M. (1975). Psychomotor skills related to driving after intramuscular administration of diazepam and meperidine. *Anesthesiology*, **42**, 685.

—— —— Ertama, P., and Häkkinen, S. (1975). Recovery and simulated driving after intravenous anesthesia with thiopental, methohexital, propanidid or alphadione. *Anesthesiology*, **43**, 291.

—— Tammisto, T., Ertama, P., Pfäffli, P., Blomgren, E., and Häkkinen, S. (1977). Recovery, psychomotor skills and simulated driving after brief inhalational anesthesia with halothane or enflurane in combination with nitrous oxide and oxygen. *Anesthesiology*, **46**, 20.

Kweekel-DeVries, W. J., Spierdijk, J., Mattie, H., and Hermans, J. M. H. (1974). A new soluble acetylsalicylic acid derivative in the treatment of postoperative pain. *Br. J. Anaesth.*, **46**, 133.

O'Grady, J., and Moncada, S. (1978). Aspirin: a paradoxical effect on bleeding-time. *Lancet*, **2**, 780.

Papatheodossiou, N. (1976). Traitement de la douleur postopératoire par l'acétylsalicylate de lysine injectable. Comparison d'efficacité de l'ASL injectable et de la pentazocine. *Méd. Hyg.*, **34**, 1262.

Rajah, S. M., Penny, A., and Kester, R. (1978). Aspirin and bleeding-time. *Lancet*, **2**, 1104.

Schöndorf, T. H. (1975). Die Wirkung von Acetylsalicyl-Lysin auf die Thrombocytenfunktion. *Klin. Wochenschr.*, **53**, 1125.

Vane, J. R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature (Lond.)*, **231**, 232.

Ventafridda, V., and Martino, G. (1976). Observations on the relationships between plasma concentration and analgesic activity of a soluble acetylsalicylic acid derivative after intravenous administration in man; in *Advances in Pain Research and Therapy*, Vol. 1 (eds J. J. Bonica and D. Albe-Fessard), p. 529. New York: Raven Press.

—— Spreavice, R. (1974). Considerations on the use of analgesic drugs in different stages of neoplastic diseases. *Int. J. Clin. Pharmacol.*, **9**, 174.

Woodbury, D. M., and Fingl, E. (1975). Analgesic-antipyretics, anti-inflammatory agents, and drugs employed in the therapy of gout; in *The Pharmacological Basis of Therapeutics* (eds L. S. Goodman and A. Gilman), p. 325. New York: Macmillan Publishing Co., Inc.

COMPARAISON DE L'ACETYLSALICYLATE DE LYSINE ET DE L'OXYCODONE ADMINISTRES PAR VOIE INTRAMUSCULAIRE POUR LE TRAITEMENT DE LA DOULEUR APRES LES INTERVENTIONS CHIRURGICALES

RESUME

L'acétylsalicylate de Lysine (LAS) est un sel soluble d'acide acétylsalicylique que l'on peut administrer d'une manière parentéralle. On a comparé des doses de 12,5 mg kg^{-1} et de 25 mg kg^{-1} de LAS à une dose de 0,15 mg kg^{-1} d'oxycodone, pour le traitement de la douleur après les interventions chirurgicales, sur 60 patients souffrant de varices. Les deux traitements ont presque entièrement soulagé les douleurs allant de modérées à graves pendant la période d'observation qui a duré trois heures. Le temps qu'il a fallu pour atteindre le point culminant de l'action a été plus long après l'administration de LAS (60–90 min) qu'après l'administration d'oxycodone (30–60 min). On n'a trouvé aucune différence significative entre les doses les plus fortes et les doses les plus faibles de LAS, ce qui laisse penser à un effet plateau. D'autres expériences cliniques à l'aide de LAS administré par voie intraveineuse et d'autres modèles de douleurs sont justifiées.

VERGLEICH ZWISCHEN I.M. LYSINAZETYLSALIZYLAT UND OXYCODON IN DER POSTOPERATIVEN SCHMERZBEKÄMPFUNG

ZUSAMMENFASSUNG

Lysinazetylsalizylat (LAS) ist ein lösliches Salz der Azetylsalizyssäure und kann parenteral verabreicht werden. LAS 12,5 mg kg^{-1} und 25 mg kg^{-1} wurde mit Oxycodon 0,15 mg kg^{-1} im Bezug auf Schmerzbekämpfung nach Krampfadernoperationen bei 60 Patienten verglichen. Beide Drogen beseitigten mässige bis schwere Schmerzen fast völlig auf die Dauer der dreistündigen Beobachtungsperiode. Die Zeit bis zur Spitzenwirkung ware bei LAS länger (60–90 min) als bei Oxycodon (30–60 min). Zwischen kleinerer und grösserer Dosis von LAS zeigten sich keine signifikanten Unterschiede, was einen Kontinuaeffekt andeutet. Weitere klinische Experimente mit LAS in intravenöser Verabreichung und mit anderen Schmerzfällen sind angezeigt.

COMPARACION ENTRE EL ACETILOSALICILATO DE LISINA I.M. Y LA OXICODONA EN EL TRATAMIENTO DEL DOLOR DESPUES DE OPERACIONES

SUMARIO

El acetilosalicilato de lisina (ASL) es una sal soluble de ácido acetilosalicílico y puede administrarse parentéricamente. Se llevó a cabo una comparación de 12,5 mg kg^{-1} y de 25 mg kg^{-1} de ASL con 0,15 mg kg^{-1} de oxicodona en el tratamiento del dolor después de la operación en 60 pacientes sometidos a cirujía de las várices. Ambos tratamientos aliviaron casi totalmente el dolor moderado a severo durante el periodo de observación de 3 h. El tiempo transcurrido hasta el punto culminante de la acción fue más largo después del ASL (60–90 min) que después de la oxicodona (30–60 min). No hubo diferencias significativas entre las dosis mayores y menores de ASL, lo que hace pensar en un efecto de nivelación. Se responde de los experimentos clínicos adicionales con ASL, al usar el método de administración i.v. y otras estructuras del dolor.

Br. J. Anaesth. (1980), **52**, 619

PERIOPERATIVE CONSIDERATIONS IN THE MANAGEMENT OF TRACHEOTOMY FOR THE OBSTRUCTIVE SLEEP APNOEA PATIENT

Three illustrative case reports

T. D. RAFFERTY, A. RUSKIS, C. SASAKI AND J. B. GEE

SUMMARY

The perioperative course of three patients with obstructive sleep apnoea who underwent tracheotomy is presented as illustrative of the potentially life-threatening complications of management. It is concluded that this disease demands strict adherence to basic principles of airway management and close observation extending into the period after operation.

The Pickwickian syndrome, a term coined by Sir William Osler (1918), was described classically by Burwell and his associates (1956). This disease is characterized by obesity, excessive daytime sleepiness, loud snoring, and cor pulmonale. However, it is now recognized that obesity is not always a necessary feature of the syndrome (Guilleminault, Tilkian and Dement, 1976). Although the defect common to all patients is apnoea during sleep, this respiratory dysfunction is not always detectable when patients are fully alert. Two types of sleep apnoea have been distinguished. The central form is associated with cessation of respiratory muscle activity and is attributed to a defect in the respiratory centre. The obstructive variety combines demonstrable respiratory muscle activity with a concomitant lack of airflow at the nose or mouth. Although many of these latter cases have an organic basis, a common cause of the obstruction is a functional disorder of the hypopharyngeal musculature. Mixed types with a combination of a central and an obstructive component occur (Glenn et al., 1976; Farmer, Glenn and Gee, 1978). Patients prone to sleep apnoea exhibit significant haemodynamic derangements in addition to the primary respiratory abnormality. These include systemic and pulmonary hypertension (Coccagna et al., 1972). The latter may lead ultimately to cor pulmonale. A variety of cardiac arrhythmias may occur during apnoeic episodes. These are associated with hypoxia and include sinus arrest, complete heart block and ventricular tachycardia (Guilleminault et al., 1975; Tilkian et al., 1975).

Patients with sleep apnoea may present many problems of anaesthetic management. Hishikawa and colleagues (1970) have described an incident in which the accidental injection of a barbiturate necessitated emergency tracheotomy in such a patient. Guilleminault and colleagues (1975) have reported a patient in whom diazepam 10 mg given i.m. twice at 1-h intervals as premedication was associated with airway obstruction. A similar observation was recorded by Simmons and co-workers (1977) following the use of a bolus of diazepam 10 mg i.v. in a patient who had received the same dose of this agent i.m. as a premedicant. Oliverio, Fermon and Abramowitz (1979) described a patient with obstructive sleep apnoea who exhibited prolonged periods of central apnoea associated with the administration of halothane. These apnoeic episodes ceased when the patient had recovered fully from anaesthesia.

The following three case reports concerning tracheotomy in patients with obstructive sleep apnoea illustrate perioperative considerations which require emphasis. Specific attention is drawn to the potentially life threatening complications of treatment.

CASE REPORTS

A 58-yr-old white male was admitted for elective tracheotomy. A polysomnographic diagnosis of obstructive sleep apnoea had been established on a previous admission when the patient had presented with incapacitating daytime somnolence.

Physical examination revealed an anxious, obese individual (130 kg), not in acute distress, with a systemic arterial pressure of 170/110 mm Hg and a heart rate of 80 beat min^{-1}. Examination of the cardiovascular, respiratory and neurological systems

---

TERENCE D. RAFFERTY, M.D.; ALAN RUSKIS, M.D.; CLARENCE SASAKI, M.D.; J. BERNARD GEE, M.D.; Yale University School of Medicine, 333, Cedar Street, New Haven, Connecticut 06510, U.S.A.

0007-0912/80/060619-04 $01.00

© Macmillan Journals Ltd 1980

revealed no abnormality. The haemoglobin concentration was 14.5 g dl^{-1}. The concentrations of the serum electrolytes were normal and the e.c.g. was within normal limits. A chest radiograph showed mild cardiomegaly. The patient was premedicated with morphine 12 mg, hydroxyzine 25 mg and atropine 0.5 mg, given i.m. 1 h before surgery. On arrival in the operating theatre area, the patient was noted to be almost totally obstructed although awake. This respiratory obstruction was relieved readily by anterior displacement of the mandible. Tracheotomy was commenced under local anaesthesia, while the patient's airway was maintained manually. The subsequent tracheotomy proceeded uneventfully, and the patient was discharged from hospital on the 4th day after operation.

A 41-yr-old Hispanic, 150-kg male presented with a 2-yr history of severe hypersomnolence. Past surgical history included an emergency tracheotomy 3 years previously at another hospital. This had been performed for severe airway obstruction in the period immediately following a tonsil biopsy. Subsequent laryngoscopy and biopsy had not revealed any demonstrable lesion and the tracheostomy was closed. The remainder of the history was unremarkable. The patient was not in acute distress. Arterial pressure was 130/96 mm Hg and heart rate was 84 beat min^{-1}. The remainder of the physical examination and the laboratory data (haemoglobin, serum electrolytes, urinalysis, chest radiograph and electrocardiogram) were within normal limits. A diagnosis of obstructive sleep apnoea was made on the basis of a polysomnographic sleep study. An elective tracheotomy under local anaesthesia was arranged. No medication was administered before operation. Because of the patient's previous incision and his extreme obesity, the tracheotomy proved to be technically difficult. The patient became agitated and developed total airway obstruction. Attempts at endotracheal intubation proved fruitless and an emergency cricothyrotomy was performed. A No. 6.0 endotracheal tube was passed through the cricothyrotomy incision. When the airway had been secured in this fashion, general anaesthesia was induced with 2.5% thiopentone 150 mg and maintained with halothane 1.5% in oxygen 5 litre min^{-1} delivered in a semi-closed system. A standard tracheotomy between the 2nd and 3rd tracheal rings was completed without difficulty.

After operation there were intermittent periods of central apnoea which occurred even when the patient was awake and fully alert. These episodes each lasted 3–4 min and occurred approximately four times per hour. Between apnoeic periods the patient's tidal volume was 500 ml. He required mechanical ventilation with the intermittent mandatory ventilation (IMV) mode (respirator rate 6 b.p.m.) to prevent hypercarbia. The apnoeic episodes decreased in duration and frequency over 6 days and uneventful weaning was accomplished by decreasing the frequency of the mandatory ventilations in conjunction with the use of an apnoea monitor. Subsequent studies of the patient's ventilatory response to carbon dioxide and oxygen failed to reveal any abnormality.

A 31-yr-old Hispanic male (152 kg) presented at Yale–New Haven Hospital in extreme respiratory distress. A diagnosis of obstructive sleep apnoea had been made during a previous admission. The patient was difficult to rouse. He suffered intermittent apnoeic episodes associated with complete airway obstruction. Arterial pressure was 150/70 mm Hg and heart rate 100 beat min^{-1}. The remaining physical examination revealed no abnormality. Haemoglobin concentration was 13.56 g dl^{-1}. Serum electrolyte concentrations and chest radiograph were within normal limits. Simultaneous ear oximetry and electrocardiographic monitoring revealed episodes of arterial oxygen desaturation to less than 40% and multiple episodes of tachy- and brady-arrhythmia. The insertion of a nasopharyngeal airway prevented audible snoring and airway obstruction and produced both a sustained increase in arterial oxygen saturation to 85% and resolution of the cardiac arrhythmias. Tracheotomy was planned. No premedication was administered, and the patient was transferred to the operating theatre breathing oxygen-enriched air and with a doctor in attendance.

Following preoxygenation, bilateral superior laryngeal nerve blocks were performed (lignocaine 1%) and the nasal mucosa was anaesthetized with 5% cocaine. Blind nasotracheal intubation was performed. Once the airway had been secured, general anaesthesia was induced with thiopentone 175 mg i.v. and maintained with halothane 1.5% in oxygen 5 litre min^{-1} in a semi-closed system. The subsequent tracheotomy was uneventful. The patient made a good recovery and was discharged 4 days after admission.

CONCLUSION

The sensitivity of these patients to sedative agents is confirmed by the first patient, who became obstructed while still awake following premedication with morphine and hydroxyzine. This event occurred in the immediate area of the operating theatre, where personnel were available to maintain the airway. Caution would dictate that the routine use of sedative premedication is contraindicated in these patients.

Respiratory obstruction in these patients may be amenable to such simple airway management as elevation of the jaw. The insertion of a nasopharyngeal airway enabled the subsequent endotracheal intubation and tracheotomy of the third patient to be elective in nature. However, such may not always be the case, as illustrated by our second report. Extreme obesity is a common feature of the disease. Furthermore, many patients have an organic obstruction as the cause of the disorder. As a consequence, non-surgical airway management may be technically difficult in these patients. In addition, tracheotomy itself may be quite difficult in the obese patient who may have a retrosternal larynx. For these reasons, we do not recommend tracheotomy without prior control of the airway by elective endotracheal intubation. Transnasal fibreoptic pharyngoscopy has been reported to be a useful investigative aid in such patients (Simmons et al., 1977). Fibreoptic endoscopy may be particularly valuable in those patients in whom a difficult intubation is anticipated.

It is important to realize that surgical excision of the causative lesion or its bypass with an endotracheal tube or tracheostomy does not preclude a subsequent ventilatory abnormality. One of our patients (No. 2) required mechanical ventilation for 6 days after operation because of prolonged periods of central apnoea. Such a ventilatory pattern had not been a feature before. Decreased airway resistance is known to be associated with a reduction in phrenic nerve activity (O'Neil, 1959; Rattenborg, 1961). It is possible that the decreased resistance afforded by a tracheostomy caused a decrease in diaphragmatic activity sufficient to exacerbate a previously subclinical central apnoeic disorder.

The following recommendations are emphasized: (1) The routine administration of sedative pre-anaesthetic medication by the ward nurse is contraindicated. Rather, careful pharmacological sedation must be given in the operating room where sudden airway embarrassment can be managed effectively. (2) Because tracheotomy is sufficiently difficult in the obese with sleep apnoea, prior endotracheal intubation is advised, allowing the surgeon sufficient time to perform an orderly tracheotomy. (3) Relief of airway obstruction may unmask a degree of central hypoventilation which was not detected before operation. Careful monitoring *after* surgery is equally important.

REFERENCES

Burwell, C., Robin, E., Whaley, R., and Bickelmann, A. (1956). Extreme obesity associated with alveolar hypoventilation: a Pickwickian syndrome. *Am. J. Med.*, **21**, 811.

Coccagna, G., Mantovani, M., Brignani, F. Parchi, C., and Lugaresi, E. (1972). Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. *Bull. Physio-path. Resp.*, 8, 1159.

Farmer, W. C., Glenn, W. W., and Gee, J. B. L. (1978). Alveolar hypoventilation syndrome: Studies of ventilatory control in patients selected for diaphragm pacing. *Am. J. Med.*, **64**, 39.

Glenn, W. W. L., Gee, J. B. L., Cole, D. R., Farmer, W., Shaw, R., and Beckman, C. (1976). Combined central alveolar hypoventilation and upper airway obstruction: Treatment by tracheostomy and diaphragm pacing. *Am. J. Med.*, **64**, 50.

Guilleminault, C., Eldridge, F. L., Simmon, F. B., and Dement, W. (1975). Sleep apnea syndrome—Can it induce hemodynamic changes? *West. J. Med.*, **123**, 7.

—— Tilkian, A., and Dement, W. C. (1976). The sleep apnea syndromes. *Ann. Rev. Med.*, **27**, 465.

Hishikawa, Y., Furuya, E., Wakamatsu, H., and Yamamoto, J. (1970). A polygraphic study of hypersomnia with periodic breathing and primary alveolar hypoventilation. *Bull. Physio-path. Resp.*, 8, 1139.

Oliverio, R. jr, Fermon, C., and Abramowitz, R. (1979). Period apnea during adenotonsillectomy. *Anesth. Analg. (Cleve.)*, **58**, 50.

O'Neil, J. J. (1959). The role of the vocal cords in human respiration. *Laryngoscope*, **69**, 1494.

Osler, W. (1918). *The Principles and Practice of Medicine*, 8th edn, p. 190. New York: Appleton.

Rattenborg, C. (1961). Laryngeal regulation. *Acta Anaesthesiol. Scand.*, **5**, 129.

Simmons, F. B., Guilleminault, C., Dement, W. C., and Tilkian, A. (1977). Surgical management of airway obstructions during sleep. *Laryngoscope*, **87**, 326.

Tilkian, A. G., Guilleminault, C., Schroeder, J. S. Lehrman, K., Simmons, F. B., and Dement, W. (1975). Sleep-induced apnea syndrome: Reversal of serious arrhythmias after tracheostomy. *Circulation*, **51**, 131.

CONSIDERATIONS PERIOPERATOIRES AU COURS D'UNE TRACHEOTOMIE EFFECTUEE SUR UN PATIENT SOUFFRANT D'APNEE OBSTRUCTIVE PENDANT LE SOMMEIL

RESUME

Le cours périopératoire de trois malades souffrant d'apnée obstructive pendant le sommeil et qui avaient subi une trachéotomie, est présenté pour illustrer les complications qui menacent virtuellement la vie pendant la conduite de l'intervention. On en conclut que cette maladie exige que l'on se conforme très strictement aux principes de base

gouvernant le traitement des voies respiratoires, de même qu'une observation très étroite se prolongeant au-delà de la durée de l'opération.

PERIOPERATIVE ERWÄGUNGEN BEI DER DURCHFÜHRUNG EINER TRACHEOTOMIE FÜR PATIENTEN MIT SCHLAFHEMMENDER APNOE

ZUSAMMENFASSUNG

Der perioperative Krankheitsverlauf von drei Patienten mit schlafhemmender Apnoe, die einer Tracheotomie unterzogen wurden, wird als Beispiel der potentiell lebensgefährlichen Komplikationen dieser Operation dargestellt. Man kommt zum Schluss, dass diese Krankheit eine strikte Befolgung der Prinzipien der Luftwegbehandlung erfordert, sowie genaue Beobachtung des Patienten auch nach der Operation.

CONSIDERACIONES PERIOPERATORIAS EN LA GESTION DE TRAQUEOTOMIA EN PACIENTE CON APNEA DEL SUEÑO OBSTRUCTIVA

Tres informes sobre un caso ilustrativo

SUMARIO

Se presenta el curso perioperatorio de tres pacientes con apnea del sueño obstructiva que fueron sometidos a traqueotomia como ilustrador de las complicaciones potenciales de la gestion que amenazan la vida. Se llega a la conclusión de que esta enfermedad exige la estricta adherencia a los principios básicos de gestión de las vías respiratorias y a la estrecha observación durante el periodo que sigue la operación.

Br. J. Anaesth. (1980), **52**, 623

PROGRESSIVE SYSTEMIC SCLEROSIS

Prolonged sensory blockade following regional anaesthesia in association with a reduced response to systemic analgesics

R. S. NEILL

SUMMARY

The anaesthetic history of a patient with progressive systemic sclerosis is reported. On each occasion large amounts of systemic analgesics were required to control pain after operation. Regional nerve block produced prolonged periods of sensory anaesthesia. Both of these features are attributed to the effect of the disease process on the peripheral vasculature. It is suggested that advantage should be taken of the prolongation of sensory anaesthesia to help control postoperative pain in such patients.

Progressive systemic sclerosis is a slowly spreading disorder of unknown aetiology, frequently grouped with the collagen diseases (systemic lupus erythematosis and polyarteritis) because there are features in common.

The early signs of progressive systemic sclerosis include Raynaud's phenomenon, the development of thin atrophic skin over the extremities, widening of the periodontal membrane and shrinkage of soft tissue around the mouth. As the disease progresses, the atrophic skin of the extremities may ulcerate. The response to sympathectomy is disappointing.

Over a period of 3 years an adult male presented on six occasions for amputation of a digit severely involved by a process considered to be a severe form of progressive systemic sclerosis. None of these procedures was extensive or prolonged (average duration 25 min) yet they all caused postoperative pain requiring large doses of analgesic drugs which, however, had minimal effect.

General anaesthesia was used on all six occasions; in four instances the anaesthetic sequence included a narcotic analgesic either in premedication or during the operative procedure; in two instances regional anaesthesia of the brachial plexus was combined with light general anaesthesia (table I).

The requirements for analgesia after operation were similar following each anaesthetic, apart from a time lag of 15–18 h on the two occasions on which regional anaesthesia was employed. The first analgesic after operation was required within 30 min of emergence from anaesthesia, followed by one or more additional doses within the next 2 h.

Anaesthetics nos 4 and 5 are illustrative of the severity of the problem. Following anaesthetic 4, control of postoperative pain was achieved only after a total dosage of papaveretum 30 mg, morphine 5 mg and diazepam 10 mg had been given over a period of 100 min. Following anaesthetic 5, the pain was so severe following sequestrectomy of a metatarsal that a sciatic nerve block was performed at 90 min after total failure to produce analgesia with pentazocine and morphine. Relief following this was instantaneous and lasted for 16 h.

DISCUSSION

Two features of this series of anaesthetics are of interest—the very prolonged period of sensory anaesthesia following regional block, and the reduced response to systemic analgesics.

Prolonged sensory anaesthesia in patients with progressive systemic sclerosis has been reported previously. Eisele and Reitan (1971) attributed the effect to severely impaired perfusion with a possible reduction in tissue pH. Lewis (1974) found that the prolongation of anaesthesia was unaffected by an infusion of low molecular weight dextran, but was decreased significantly following an infusion of sodium bicarbonate. As tissue pH was not measured it was not possible to determine whether this decrease was the result of an alteration in tissue pH or improved perfusion.

The sympathetic nervous system and the motor and sensory components of the peripheral nervous system are all involved in the disease process. Henriksen, Kristensen and Wadskov (1977) found a decreased or absent vasoconstrictor response to an

---

R. S. NEILL, M.D., F.F.A.R.C.S.(I), Glasgow Royal Infirmary, Glasgow G4 0SF.

0007–0912/80/060623–03 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Details of surgical procedure, premedication, anaesthesia and analgesia used on six occasions for a patient with progressive systemic sclerosis*

Operation	Premedication	Anaesthesia	Analgesia after operation
Amputation (L) ring, little (R) middle fingers (30 min)	Pethidine 50 mg Promethazine 50 mg Hyoscine 0.4 mg	Althesin, halothane, DF 118 50 mg	Pethidine 100 mg, 30 min Pethidine 100 mg, 240 min
Amputation (R) index finger (25 min)	Pethidine 50 mg Promethazine 50 mg	Thiopentone, halothane	Pentazocine 50 mg, immediately Pentazocine 50 mg, 40 min Pethidine 50 mg, 100 min
Amputation (L) thumb (15 min)	None	Thiopentone, halothane, supraclavicular brachial plexus block	Pentazocine 50 mg, 920 min Pethidine 50 mg, 950 min
Amputation (R) ring finger (45 min)	Pethidine 50 mg Promethazine 50 mg	Thiopentone, halothane, fentanyl 0.1 mg	Papaveretum 20 mg, 10 min Diazepam 10 mg, papaveretum 10 mg, 60 min Morphine 5 mg i.v., 100 min Papaveretum 20 mg, 240 min
Sequestrectomy 4th (L) metatarsal (15 min)	None	Thiopentone, halothane, pentazocine 60 mg	Pentazocine 50 mg, 15 min Morphine 10 mg i.v., 75 min Sciatic nerve block, 90 min Morphine 10 mg, 960 min
Amputation (R) thumb (25 min)	None	Thiopentone, halothane, supraclavicular brachial plexus block	DF 118, 1000 min Physeptone 5 mg, 1120 min

increase in venous transmural pressure and attributed this to a sympathetic neuropathy.

Christopher and Robinson (1972) found a decrease in conduction velocity in both sensory and motor peripheral nerves. These authors suggested that the peripheral neuropathy was the result of impairment of the blood supply to the nerves, a conclusion which seems to be borne out by a recent report by Cormane, Hamerlinck and Nunzie (1978) which postulates that the primary event in progressive systemic sclerosis is an immunological attack on the peripheral parts of the vascular system.

Histological studies of the skin of patients with progressive systemic sclerosis have shown an increased number of nerve endings per unit area (Milne, 1972). The possibility that stimulation of a disproportionate number of nerve endings following surgery might explain the decrease in the response to systemic analgesics was considered, and that this might be reflected in an alteration in two-point discrimination. This was tested and was found to be within the normal range (Gellis and Pool, 1977).

Advanced degenerative arterial disease is frequently associated with necrosis of the extremities requiring amputation of digits or portions of limbs: after surgery the patient's pain can be controlled with simple analgesics. However, patients with severe rest pain do not respond to large doses of systemic analgesics, yet show an immediate response to paravertebral nerve block with local anaesthetics or ablative agents (M. E. Coull, 1979, personal communication).

It is concluded that the intense pain following surgery in this patient with progressive systemic sclerosis was ischaemic in nature—the lack of response to systemic analgesics and immediate response to sciatic nerve block mirroring the effects of rest pain in advanced degenerative arterial disease.

The prolonged period of sensory anaesthesia in this patient and in others with progressive systemic sclerosis is likely to be a result of impaired blood supply to the peripheral nerve—the explanation previously advanced to account for the peripheral neuropathy.

The patient in this report was considered to suffer from a very severe and atypical form of progressive systemic sclerosis and his response to pain may not be the same as that of other patients with the disease. However, it has not been possible to trace any patients requiring similar surgery to compare their response to analgesics or regional nerve block.

The condition is extremely rare. An average of one new case per year is referred to the Dermatology Units of the major teaching hospitals in Glasgow, each having approximately 4000 new referrals per year.

CONCLUSION

The inclusion, when possible, of a regional nerve block in the anaesthetic regime for patients with progressive systemic sclerosis would seem to be advantageous, providing a prolonged period of analgesia after surgery. The author (Neill, 1978) has found previously that simple analgesics were adequate following regional block for hand surgery, but this would not appear to be the case in patients with progressive systemic sclerosis.

ACKNOWLEDGEMENTS

My thanks are due to Drs W. Richards and D. W. Ferguson, for permission to use anaesthetic records; Professor Rona MacKie for criticism and advice; Mr I. A. McGregor for permission to publish details of cases under his care and Mrs A. M. Allanach for secretarial assistance.

REFERENCES

Christopher, R. P., and Robinson, H. (1972). Studies of nerve conduction in patients with scleroderma. *South. Med. J.*, **65**, 668.

Cormane, R. H., Hamerlinck, F., and Nunzie, E. (1978). Elution of antibodies from the lymphoid cell membrane in certain varieties of scleroderma. *Progress in Cutaneous Immunopathology*, 6th Symposium, Lyon. F. R. A. Inserm, No. 11, p. 133.

Eisele, J. H., and Reitan, J. A. (1971). Scleroderma, Raynaud's phenomenon and local anesthetics. *Anesthesiology*, **34**, 386.

Gellis, M., and Pool, R. (1977). Two point discrimination distances in the normal hand and forearm. *Plast. Reconstr. Surg.*, **59**, 57.

Henriksen, O., Kristensen, J. K., and Wadskov, S. (1977). Local regulation of blood flow in subcutaneous tissue in generalized scleroderma. *J. Invest. Dermatol.*, **68**, 318.

Lewis, G. B. H. (1974). Prolonged regional anaesthesia in scleroderma. *Can. Anaesth. Soc. J.*, **21**, 495.

Milne, J. A. (1972). *An Introduction to the Diagnostic Histopathology of the Skin*, chapter 9, p. 178. London: Arnold.

Neill, R. S. (1978). Postoperative analgesia following brachial plexus block. *Br. J. Anaesth.*, **50**, 379.

SCLEROSE SYSTEMIQUE PROGRESSIVE

Blocage sensoriel prolongé à la suite d'une anesthésie regionale, associé à une reponse affaiblie aux analgésiques systémiques

RESUME

Il est fait rapport au sujet du dossier anesthétique d'un malade souffrant de sclérose systémique progressive. Dans chaque cas, de grandes quantités d'analgésiques systémiques ont été nécessaires pour contrôler la douleur après l'operation. Le blocage régional des nerfs a eu pour effet de longues périodes d'anesthésie sensorielle. On attribue ces deux caractéristiques à l'effet du processus de la maladie sur la vasculature périphérique. On suggère qu'il convient de tirer parti de la prolongation de l'anesthésie sensorielle pour faciliter le contrôle de la douleur postopératoire chez de tels malades.

DIE PROGRESSIVE ALLGEMEINE SKLEROSE

Anhaltende sensorische Blokierung infolge von Lokalanästhesie in Verbindung mit vermindertem Ansprechen auf allgemeine Analgesie

ZUSAMMENFASSUNG

Es wird über die Anästhesie-Vorgeschichte eines Patienten mit progressiver allgemeiner Sklerose berichtet. Bei jeder Anästhesie wurden grosse Mengen von allgemeinen Betäubungsmitteln benötigt, um die postoperativen Schmerzen zu bekämpfen. Örtliche Blockeirung der Nerven führte zu ausgedehnten Perioden von sensorischer Anästhesie. Beide Zustände sind auf die Auswirkung des Krankheitsprozesses auf das periphere Gefässsystem zurückzuführen. Es wird vorgeschlagen, dass die Verlängerung der sensorischen Anästhesie ausgenutzt werden sollte, um bei solchen Patienten die postoperativen Schmerzen zu bekämpfen.

ESCLEROSIS SISTEMICA PROGRESIVA

Bloqueo sensorio prolongado a raiz de una anestesia regional asociado con una respuesta reducida a analgesicos sistémicos

SUMARIO

Se informa sobre el historial anestético de un paciente con esclerosis sistémica progresiva. En cada oportunidad, fueron necesarias grandes cantidades de analgésicos sistémicos para controlar el dolor después de la operación. El bloqueo nervioso regional ocasionó periodos prolongados de anestesia sensoria. Ambos rasgos se atribuyen al efecto de la enfermedad sobre la vasculatura periférica. Se sugiere que se aproveche de la prolongación de la anestesia sensoria para facilitar el control de dolor postoperatorio en tales pacientes.

Br. J. Anaesth. (1980), **52**, 627

A SIMPLE AND INEXPENSIVE DEVICE FOR ADMINISTRATION OF CONTINUOUS POSITIVE AIRWAY PRESSURE BREATHING

M. BAGGER

SUMMARY

A simple system for administration of continuous positive airway pressure breathing uses a corrugated hose in the modified Mapleson D system for anaesthesia. The only mechanical component of the system is a spring-loaded valve for positive end expiratory pressure.

Continuous positive airway pressure (CPAP) was introduced by Gregory and others (1971) in the treatment of neonates with respiratory distress syndrome (RDS). The method has been modified by Civetta, Brons and Gabel (1972) in the treatment of the adult RDS.

The positive pressure in the system depends on the flow rate and (expiratory) resistance. In adults with RDS, high flows of gas (15–20 litre min^{-1}) have been used to prevent rebreathing.

Considerable pressure variations have occurred in the systems previously described. Thus Andersen, Brøckner and Beck (1975) with a preset pressure of 10 cm H_2O found a variation of 8–10 cm H_2O.

The present system has been designed to reduce pressure variation and avoid rebreathing in a simple system.

METHODS AND RESULTS

Fresh gas passed from a flowmeter through the central part (F) of a coaxial hose with a modified Mapleson D system (Bain and Spoerel, 1972) (fig. 1). The gas outlet was placed as close as possible to a mouth-piece (A) with sampling sites (S) (for pressure and carbon dioxide measurement). Expired gas and excess fresh gas were led through the external part of the coaxial hose. The other end of the hose was connected to a spring-loaded expiratory valve (V) with a variable-resistance (PEEP-valve, Ambu International) and a latex-rubber bag (R) with the volume of 5.5 litre.

The coaxial hose acted as a one-way valve and, in combination with the bag as a pressure buffer, reduced pressure variations during inspiration and expiration.

The original length of the coaxial hose (130 cm) reduced the role of the bag as a pressure buffer because of the flow resistance in the hose. Therefore the hose was shortened to 40 cm. In our experiment flow was kept constant at 15 litre min^{-1} and variation in pressure was made only by changing the expiratory resistance. The overall volume of the system was 5.7 litre. The volume of the coaxial hose was 0.15 litre.

Pressure was measured at the mouth-piece with a Statham PT5C differential pressure transducer connected to an amplifier (Ellab type M5 BCM A). Carbon dioxide concentration was measured with an infra-red carbon dioxide analyser (Capnograph, Godart–Mijnhardt). Both measurements were recorded on a three-channel recorder (Mingograf 34, Siemens–Elema). Pressure variations were measured over at least 15 breaths. Mean pressures were calculated by planimetry.

The system was tested on eight healthy adult volunteers (four men and four women). Before the investigation each subject received instruction to ensure normal breathing and correct application of the mouth-piece and the nose-clip.

Static pressure was preset at 7.5, 10 and 15 cm H_2O respectively by variation of the expiratory resistance with the mouth-piece closed.

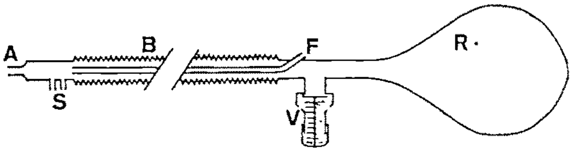


FIG. 1. CPAP breathing device: A = mouth-piece; S = sampling sites for pressure and carbon dioxide monitoring; B = coaxial hose; F = central part of coaxial hose; V = spring-loaded expiratory valve; R = expandable rubber bag.

MOGENS BAGGER, M.D., Department of Anaesthesiology, Centralsygehuset, DK 8900 Randers, Denmark.
Present address: Embedslægeinstitutionen for Ringkøbing Amt. Østergade 52, 6950 Ringkøbing, Denmark.

0070–0912/80/060627–02 $01.00

© Macmillan Journals Ltd 1980

TABLE I. *Results in eight adult volunteers. The range of pressure was measured over a minimum of* 15 *breaths.* Δp = *inspiratory–expiratory difference*

Subject no.	Static pressure (cm H_2O)								
	7.5			10			15		
	Range	Δp	Mean	Range	Δp	Mean	Range	Δp	Mean
1	4.4–8.0	3.6	7.2	8.0–10.8	2.8	9.6	13.0–15.0	2.0	14.4
2	6.0–9.2	3.2	7.6	7.2–11.2	4.0	10.0	12.0–14.8	2.8	14.0
3	4.0–8.8	4.8	6.8	7.6–10.8	3.2	9.6	12.0–14.8	2.8	14.0
4	2.8–7.6	4.8	5.6	4.0–8.8	4.8	6.8	9.6–12.8	3.2	12.0
5	2.4–8.0	5.6	6.0	4.0–9.2	5.2	8.0	10.0–13.0	3.0	12.0
6	2.4–8.0	5.6	6.0	6.0–10.0	4.0	6.0	12.0–14.4	2.4	13.2
7	2.2–8.0	5.2	6.0	3.2–10.0	6.8	7.6	11.6–14.4	2.8	12.8
8	3.6–7.6	4.0	6.0	7.2–10.8	3.6	9.6	11.6–14.4	2.8	13.2

After presetting the respiratory resistance the volunteer breathed for 5 min at pressures of 7.5 and 10 cm H_2O and for 10 min at a pressure of 15 cm H_2O before measurements.

The inspiratory and expiratory concentrations of carbon dioxide were constant throughout.

Pressure variations and calculated mean pressures are shown in table I.

DISCUSSION

The largest differences between inspiratory and expiratory pressure were found at static pressures of 7.5 and 10 cm H_2O, while the differences at a static pressure of 15 cm H_2O were significantly smaller ($P < 0.01$ Pratt's test). This was probably a result of the compliance of the rubber bag.

Acceptable mean pressures were obtained with the present system. Furthermore, pressure variation during breathing was minimized compared with other systems (Andersen, Brøckner and Beck, 1975). In the treatment of adults with RDS it has been the practice to use greater pressures in CPAP breathing. Thus the very small variations in pressure (2–3 cm H_2O) at a static pressure of 15 cm H_2O adds further advantage to the system.

Apart from the bag, the system may be assembled easily from commonly available components. For clinical purposes a humidifier should be added and it is suggested that pressures be recorded with a simple anaeroid manometer.

REFERENCES

Andersen, J., Brøckner, J., and Beck, O. (1975). Intermittent positive end expiratory pressure (PEEP) in the treatment of atelectasis. *Ugeskr. Laeg.*, **137**, 889.

Bain, J. A., and Spoerel, W. E. (1972). A streamlined anaesthetic system. *Can. Anaesth. Soc. J.*, **19**, 426.

Civetta, J. M., Brons, R., and Gabel, J. C. (1972). A simple and effective method of employing spontaneous positive-pressure ventilation. *J. Thorac. Cardiovasc. Surg.*, **63**, 112.

Gregory, G. A., Kitterman, J. A., Phibbs, R. H., Tooley, W. H., and Hamilton, W. K. (1971). Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. *N. Engl. J. Med.*, **284**, 1333.

DISPOSITIF SIMPLE ET BON MARCHE POUR L'ADMINISTRATION DE RESPIRATION SOUS PRESSION POSITIVE CONTINUE AUX VOIES RESPIRATOIRES

RESUME

Un système simple pour l'administration de respiration sous pression positive continue aux voies respiratoires, comporte un tuyau coaxial ondulé du système Mapleson-D modifié pour l'anesthésie. Le seul organe mécanique du système est une soupape à ressort pour la pression positive de fin d'expiration.

EINE EINFACHE UND BILLIGE VORRICHTUNG ZUR VERABREICHUNG EINER KONTINUIERLICHEN, POSITIVEN DRUCKBEATMUNG

ZUSAMMENFASSUNG

Ein einfaches System zur Verabreichung einer kontinuierlichen, positiven Druckbeatmung der Luftwege bedient sich eines welligen Koaxialschlauches für das modifizierte Mapleson D System der Narkose. Der einzige mechanische Bestandteil des Systems ist ein Federventil für positiven Endausatmungsdruck.

UN DISPOSITIVO SENCILLO Y BARATO PARA LA ADMINISTRACION DE RESPIRACION POR PRESION RESPIRATORIA POSITIVA Y CONTINUA

SUMARIO

En el sistema Mapleson D modificado de anestesia, un sistema sencillo de administración de respiración por presión respiratoria positiva y continua use una manguera coaxial acanalada. El único componente mecánico del sistema consiste en una válvula de resorte para la presión espiratoria terminal positiva.

Br. J. Anaesth. (1980), 52, 629P

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

NOTTINGHAM MEETING

MARCH 21, 1980

COMPUTER-ASSISTED DECISION MAKING IN ANAESTHESIA

M. J. Harrison and F. Johnson
Department of Surgery (Anaesthesia and Orthopaedics), Queen's Medical Centre, Nottingham

The use of computers in the control of the depth of anaesthesia has been examined (Mapleson et al., 1979), but no general application in clinical anaesthesia has been identified. A program has been designed to aid the anaesthetist in a practical way and enhance the safety of the patient.

The patient's clinical details are entered into the computer in response to the computer suggesting possible clinical situations in a systematic way—urgency of procedure, age of patient, medical problems, surgical requirements and coexistent drug therapy.

Instructions, or advice, are stored in the computer under the six headings of "preparation", "premedication", "induction/intubation", "maintenance and reversal", "postoperative care" and "drug interactions".

The clinical details are first matched with a set of usage codes for each of the advice statements. Matching codes cause the particular advice to be stored temporarily. Instructions can also be given for combinations of clinical conditions or advice, or both.

A hierarchy of recommendations is used which includes "Avoid", "Specially recommended" and "Use". Each of the advice statements is examined in turn, treatments to avoid are eliminated, and then a final list of instructions is printed in a collated form under the six headings.

The two parts of the program are run on a Digital Equipment Corporation MINC-11 system which has 64 K bytes of memory and two 0.5-M byte diskettes. The programs are written in FORTRAN, and run under the RT-11 operating system. About 24 K bytes of memory are needed for storage of the data files for each part of the program.

The method can be used with an inexpensive desk-top computer. Such a system may be used within a theatre complex to identify problems which may be outside the anaesthetist's own personal experience, and to suggest possible solutions.

REFERENCE

Mapleson, W. W., Chilcoat, R. T., Lunn, J. N., Blewett, M. C., Khatib, M. T., and Willis, B. A. (1979). *Br. J. Anaesth.*, 52, 234P.

ASSESSMENT OF POSTOPERATIVE PERFORMANCE DECREMENT USING A SERIAL FOUR-CHOICE REACTION-TIME TEST

Andrew Scott and J. G. Whitwam
Royal Postgraduate Medical School, London
R. T. Wilkinson and J. E. J. Whitten
M.R.C. Applied Psychology Unit, Cambridge

The assessment of performance in subjects recovering from short surgical procedures has been limited by a lack of practical methods. The present study was undertaken to evaluate the "four-choice reaction time" test described by Wilkinson and Houghton (1975).

Three groups of subjects were studied: a control group comprising nine women admitted to hospital for bed rest during the first 20 weeks of pregnancy, and a further two groups of subjects receiving general anaesthesia for short gynaecological procedures. The anaesthetic sequence was either thiopentone, followed by nitrous oxide, oxygen and halothane (10 women) or methohexitone and fentanyl, followed by nitrous oxide, oxygen and incremental methohexitone (13 women).

The tests, each of 5 min duration, were given on seven occasions to each subject: twice on the day before operation, between 16.00 and 19.00 h; on the day of operation approximately 2, 4, 6 and 8 h after operation; and finally the following day 24 h after operation. The results were recorded on magnetic tape and analysed subsequently to find average reaction time, coefficient of variation, percentage errors and number of "blocks" (reaction time > twice the average). The first test before operation was used as a practice test only. Performance decrement on the day of operation was calculated as the difference from the average value the day before and the day after.

Mean average reaction times of the control subjects on the first day (before operation) was 532.7 ms. It decreased to 509.6, 497.7, 495.1 and 486.3 ms at 11.00, 13.00, 15.00 and 17.00 h respectively the following day and was 464.7 ms at 09.00 h on the 3rd day. The average reaction time of the subjects receiving thiopentone was 528.0 ms before operation and increased to 575.3, 546.8, 520.8 and 530.2 ms approximately 2, 4, 6 and 8 h after operation. Twenty-four hours after operation it had decreased to 477.5 ms. Average reaction time of the methohexitone subjects was 522.1 ms before operation and increased to 599.9, 546.5 and 526.3 ms after 2, 4 and 6 h and decreased to 509.5 and 475.9 ms after 8 and 24 h respectively. Statistical analysis using the non-parametric Wilcoxon test showed that there was a significant ($P < 0.01$) performance decrement 4 and 6 h following anaesthesia in the thiopentone group and at 2 h following anaesthesia in those receiving methohexitone. Inspection of the changes in error rate, number of blocks and variability of reaction time showed no reliable trend in these variables.

It was concluded that the average reaction time in a four-choice test is a useful measure of the duration and degree of postoperative performance decrement following different anaesthetic techniques.

REFERENCE

Wilkinson, R. T., and Houghton, D. (1975). *Behav. Res. Meth. Instrum.*, 7, 441.

CHANGES IN COLLOID OSMOTIC PRESSURE AND PLASMA ALBUMIN ASSOCIATED WITH EXTRACORPOREAL CIRCULATION

R. Sanchez de Leon, Jennifer L. Paterson and M. K. Sykes
Department of Anaesthetics, Royal Postgraduate Medical School, Du Cane Road, London

Colloid osmotic pressure (COP), plasma albumin concentration, haematocrit and blood-gas tensions were measured in 16 patients undergoing open-heart surgery with cardiopulmonary bypass. The use of crystalloid priming and cardioplegia solutions resulted in a 60% reduction in COP, a 48% reduction in plasma albumin and a 34% reduction in haematocrit. These measurements had returned to pre-perfusion values 6 h after the end of surgery. The alveolar-arterial $P\text{O}_2$ difference increased significantly after bypass and returned to pre-perfusion values within the same time scale. Right-to-left shunt was significantly increased 30 min after the end of bypass. It is suggested that the changes are produced by interstitial pulmonary oedema associated with the reduction in COP.

In six of these patients and in 11 other patients undergoing open-heart surgery, the mean right-to-left shunt increased from 7.5 to 9.5% of the cardiac output. One patient developed an increase in shunt from 9 to 22% after bypass and required high inspired oxygen concentrations and mechanical ventilation of the lungs with positive end-expiratory pressure. It was concluded that the small values of COP recorded in these patients do not normally cause interstitial or alveolar oedema, provided that pulmonary vascular pressures remain within normal limits.

A SIMPLE METHOD TO DETERMINE THE SOLUBILITY COEFFICIENT OF ACETYLENE IN BLOOD

C. G. Male
Department of Postgraduate Medicine, University of Keele

The original method to determine the blood-gas solubility of acetylene involved the manometric apparatus of Van Slyke and Haldane (Grollman, 1929). Despite numerous attempts, the author has been unable to reproduce these experiments to determine the unpublished Bunsen solubility coefficient for acetylene in sheep blood. Another method of analysis of multiple foreign gases by gas chromatography after equilibration of the sample with helium (Wagner, Naumann and Laravuso, 1974) was unavailable. This stimulated the development of the following method.

Heparinized whole blood was tonometered with nitrogen for 20 min at 37 °C. One millilitre of blood was drawn anaerobically into a 2-ml ungreased glass syringe, weighed and injected into a closed 17-ml mixing flask for equilibration with purified acetylene fully saturated with water, and agitated in a waterbath at 37 °C. The volume of gas absorbed by the blood sample was measured by the movement of a mercury meniscus in a horizontal 1-ml (1/100) glass serological pipette connected to the flask by a three-way tap. The distal end of the pipette was open to the atmosphere. Corrections were applied for the equilibration of nitrogen in the blood sample with the gas phase, loss of gas from the apparatus during the experiment and the weight gains and losses of the mixing flask and syringe after transfer of the blood sample.

Sixty separate experiments were performed on venous blood drawn from 10 human volunteers and the same on venous blood from 10 sheep. The Bunsen solubility coefficient of acetylene determined by this method was acetylene 0.717 (± 1 SD 0.020) ml STPD ml^{-1} blood at 37.0 °C for man and acetylene 0.678 (± 1 SD 0.024) ml STPD ml^{-1} blood at 39.0 °C for sheep. Within-subject variance was 0.00058 and 0.00083, and between-subject variance 0.00013 and 0.00008 respectively for man and sheep. Between-subject mean values showed no correlation with common haematological and biochemical parameters.

The experimental error of the manometric apparatus of Van Slyke and Haldane has not been described. That observed by Wagner with the gas chromatograph was twice that of the method described above. This method requires only basic laboratory equipment and minimal training to determine reliably the solubility coefficient of acetylene in blood taken from different individuals and species.

ACKNOWLEDGEMENT

This work was supported by the Medical Research Council of New Zealand.

REFERENCES

Grollman, A. (1929). *J. Biol. Chem.*, **82**, 317.
Wagner, P. D., Naumann, P. F., and Laravuso, B. (1974). *J. Appl. Physiol.*, **36**, 600.

RELATIONSHIP OF INTERVAL BETWEEN ADMINISTRATIONS TO ENZYME CHANGES FOLLOWING REPEAT HALOTHANE AND ENFLURANE

J. W. Dundee, G. W. Black, D. S. C. Bradley and J. R. Doggart
Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland

In a prospective study, Fee and colleagues (1979) have demonstrated a greater frequency of abnormal liver enzyme activity following repeat halothane than following enflurane. However, they omitted to relate the frequency of changes to the time interval between administrations. Because of the small number of positive findings such an analysis was only possible with gamma glutamyl transferase (GGT) and alanine amino transferase (ALT), and even with these the number of patients was very small in some groups (table I).

TABLE I. *Frequency of abnormal concentrations of GGT following repeat halothane and enflurane anaesthesia*

Interval between 1st and 2nd anaesthetic (weeks)	Halothane	Enflurane
1–6	8/16	4/16
7–12	3/17	1/10
13–17	3/13	3/16
18–30	5/17	4/24
Total	19/63 (30%)	12/66 (18%)

With both agents, patients who were anaesthetized within the previous 6 weeks had a significantly greater frequency of abnormal GGT and ALT activity ($P < 0.005$) than those with an interval of 7–30 weeks. There were only eight ALT abnormalities in the halothane series, of which 4/16 (25%) were in the 1–6-week group compared with 4/47 (9%) where the interval between administrations was more than 6 weeks.

Of the 22 patients who had a third administration of halothane, with a 6–12-week interval between administrations, GGT abnormalities were found in 4/10, compared with 2/12 with a 13–21-week interval.

A short interval between administrations would appear to be a contributing factor in the aetiology of liver enzyme changes following repeat anaesthetics.

REFERENCE

Fee, J. P. H., Black, G. W., Dundee, J. W., McIlroy, P. D. A., Johnston, H. M. L., Johnston, S. B., Black, I. H. C., McNeill, H. G., Neill, D. W., Doggart, J. R., Merrett, J. D., McDonald, J. R., Bradley, D. S. G., Haire, M., and McMillan, S. A. (1979). *Br. J. Anaesth.*, **51**, 1133.

EFFECT OF HALOTHANE ON THE PERFORMANCE OF THE HEART IN THE CASE OF CRITICAL CONSTRICTION OF THE LEFT CIRCUMFLEX CORONARY ARTERY

C. M. FRANCIS, C. GLAZEBROOK, E. LOWENSTEIN*, W. L. DAVIES, P. FOËX AND W. A. RYDER
*Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford (*Present address: Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts)*

It has been shown that halothane may cause severe contraction abnormalities in regions of myocardium supplied by a narrowed coronary artery. If the area supplied by the narrowed vessel is small, this dysfunction may not be reflected by changes in global myocardial performance (Francis et al., 1980). In the case of narrowing of an artery supplying a large area of the left ventricular wall, depression of global myocardial function could be expected to be of the same magnitude as depression of regional function.

In seven dogs, the effects of stepwise increases of halothane concentration (0.5–2% in increments of 0.25%) on global and regional function have been studied before and after constriction of the left circumflex coronary artery (LC). Regional function was evaluated using miniature ultrasonic length transducers implanted in the subendocardial muscle supplied by either LC or the left anterior descending (LAD) coronary artery. The main LC was constricted close to its origin by a micrometer-controlled snare. E.c.g., aortic, left ventricular and left atrial pressures, LV dP/dt and length signals were recorded as well as aortic and left coronary blood flow (electromagnetic flowmeters). The use of coronary flow measurement allows a more precise definition of critical constriction. It is now defined as the maximum amount of tightening of the snare, compatible with normal regional function, that prevents 95% of the peak hyperaemic response to a 10-s occlusion of the vessel.

Dose-dependent reductions of mean arterial pressure (up to 48%), LV dP/dt max (up to 60%), cardiac output (up to 55%), rate pressure product (up to 51%) and increases of LVEDP (up to 3.3 kPa) were observed in response to increasing concentrations of halothane before constriction of LC.

After constriction of LC, at 0.5% halothane, global and regional function were maintained. Increasing halothane concentrations, however, caused irreversible myocardial depression in five dogs. Irreversible depression was observed in one dog at 1.5% halothane, in two dogs at 1.75% halothane and in two dogs at 2% halothane. After critical constriction of a coronary artery the primary determinant of blood flow is the perfusion pressure, (MAP − LVEDP). The dose-related decrease of MAP and increase of LVEDP brought about by stepwise increases of halothane will, therefore, lead to a decrease in coronary blood flow, which may become too small to meet the oxygen requirements of the segment supplied. In this case contraction will be impaired. The LC segment comprises such a large part of the left ventricular wall that any decrease in its performance is reflected in global performance. Any impairment of global performance will further decrease coronary perfusion pressure. In the five dogs that died, we observed an initial deterioration in the LC segment, which was followed rapidly by severe loss of regional and global function.

These experiments indicate that critical constriction of a coronary artery supplying a large area of the myocardium may cause severe loss of regional myocardial performance that is accompanied by an equally severe loss of global performance. This is at variance with observations made after critical constriction of the LAD where there is a dissociation between regional and global performance.

ACKNOWLEDGEMENT

C. M. Francis is in receipt of an M.R.C. Research Studentship.

REFERENCE

Francis, C. M., Lowenstein, E., Davies, W. L., Foëx, P., and Ryder, W. A. (1980). *Br. J. Anaesth.*, **52**, (in press).

HUMAN VOLUNTEER STUDIES OF R 39209, A NEW SHORT-ACTING NARCOTIC ANALGESIC

B. KAY AND B. PLEUVRY
Department of Anaesthetics, University of Manchester

The effects of R 39209 were studied in five volunteers. Doses of 1.6, 3.2 and 6.4 $\mu g\,kg^{-1}$ were compared in a controlled, randomized investigation.

Spirometry revealed that R 39209 6.4 $\mu g\,kg^{-1}$ induced respiratory depression of early onset and short duration, with significant reduction of mean minute volumes at 3 and 4 min after i.v. injection. Saline and smaller doses of R 39209 had no significant effect on ventilation. Mean end-expired carbon dioxide concentration was increased significantly from 2 to 9 min after injection of R 39209 6.4 mg kg^{-1}, highly significant increases occurring at 3, 4 and 5 min.

The transient effect of R 39209 was confirmed by the fact that no change in mean ventilatory response to carbon dioxide was demonstrable 30 or 50 min after any dose.

There was no significant change in mean heart rate, systolic or diastolic arterial pressure after any medication.

Every volunteer was able to recognize when R 39209 had been administered, and to distinguish between the three doses used. The short-lived subjective effects were typical of the opiates, including sensations of flushing, warmth, slight dizziness and sleepiness. One volunteer in pain perceived an analgesic action. In one volunteer the sensations produced dysphoria, the others became euphoric. No nausea or vomiting was experienced. R 39209 produced a transient dose-related meiosis.

In a separate controlled, randomized, single-blind investigation in five volunteers the effect of R 39209 on ventilatory response to carbon dioxide was studied. Response curves obtained at 1 min after i.v. injection of R 39209 1.6, 3.2 and 6.4 μg kg^{-1} showed a dose-related shift to the right.

VENTILATORY DEPRESSION RELATED TO PLASMA FENTANYL CONCENTRATIONS DURING AND AFTER ANAESTHESIA

K. J. Gill, D. P. Cartwright, A. Scoggins, A. J. Gray and C. Prys-Roberts
University Department of Anaesthetics, Medical School, Bristol

The use of medium to large doses of fentanyl (10–25 μg kg^{-1}) may be followed by prolonged ventilatory depression after operation, and has been associated with ventilatory arrest (Adams and Pybus, 1978). Hypocapnia may reduce fentanyl requirements, but the relationship between plasma fentanyl concentration and ventilatory effects has not been clarified in man.

This study was designed to measure the ventilatory responses associated with the plasma fentanyl concentrations obtained at various times after a single bolus dose of fentanyl either 10 μg kg^{-1} or 25 μg kg^{-1} in patients ventilated during surgery to normocapnia or hypocapnia. Patients were premedicated with fentanyl 1.5 μg kg^{-1} and anaesthesia was induced with the allocated dose of fentanyl followed by a sleep dose of Althesin if necessary. Intubation of the trachea followed muscle relaxation with pancuronium 0.5 mg kg^{-1} and the lungs were ventilated with nitrous oxide and oxygen (ratio 2:1). Four groups of six patients were allocated randomly as follows:

group I—fentanyl 10 μg kg^{-1}, Pa_{CO_2} 5.0–5.6 kPa;
group II—fentanyl 25 μg kg^{-1}, Pa_{CO_2} 5.0–5.6 kPa;
group III—fentanyl 10 μg kg^{-1}, Pa_{CO_2} 2.6–3.3 kPa;
group IV—fentanyl 25 μg kg^{-1}, Pa_{CO_2} 2.6–3.3 kPa.

The effect of fentanyl on ventilation was assessed by measuring the change in slope and position of carbon dioxide response curves relating mouth occlusion pressures or expired minute volume to carbon dioxide concentrations during rebreathing (Matthews and Howell, 1975). Control measurements were made 1 or 2 days before operation, and further measurements made immediately before induction, at the end of surgery and before and after an analgesic dose of fentanyl in the recovery ward. Blood-gas tensions were measured on arterial blood samples at the same times. Plasma fentanyl concentrations were measured by radioimmunoassay.

The pharmacokinetic data for all the groups were in agreement with previously published work, and we found no evidence of peaks of fentanyl concentration in the plasma which deviated from the exponential decay of the slow elimination phase. No evidence was found to substantiate the findings in dogs (Ainslie, Eisele and Corkill, 1979) that hypocapnia was associated with an impaired elimination of fentanyl.

At the end of surgery, no significant depression of carbon dioxide response could be detected in patients receiving 10 μg kg^{-1} (groups I and III). Carbon dioxide response curves were depressed ($P < 0.05$) in both groups of patients receiving 25 μg kg^{-1} (groups II and IV), and in the hypocapnic patients (group IV) this depression persisted into the period after operation. Despite the varying degrees of depression of the carbon dioxide responses, Pa_{CO_2} values greater than 6.0 kPa were found in only four patients, all in groups II or IV. A significant relationship ($r = 0.83$) was found between the slope of the carbon dioxide response curve (as a percentage of the awake control slope) and Pa_{CO_2}, which indicated that Pa_{CO_2} values in excess of 6.0 kPa were found only if the slopes of the carbon dioxide response curve were depressed by more than 50% of the awake value. In patients in group IV, 50% depression of the carbon dioxide response curve occurred at smaller plasma fentanyl concentrations than in group II, suggesting that hypocapnic ventilation during anaesthesia may have enhanced ventilatory depression in the period after operation. Differences between patients in groups I and III were small but followed the same trend.

REFERENCES

Adams, A. P., and Pybus, D. A. (1978). *Br. Med. J.*, **1**, 278.
Ainslie, S. G., Eisele, J. H. jr, and Corkill, G. (1979). *Anesthesiology*, **51**, 293.
Matthews, S. G., and Howell, J. B. L. (1975). *Clin. Sci. Molec. Med.*, **49**, 57.

A PHARMACODYNAMIC MODEL FOR FAZADINIUM

C. J. Hull, M. J. M. English and A. Sibbald
Department of Anaesthesia, University of Newcastle upon Tyne

Although fazadinium appears to have a duration of action comparable to that of pancuronium, it has a very short latency and a rapid decay of plasma concentration after single doses (Duvaldestin et al., 1978). In order to define the relationships between dose and effect more precisely, a simple pharmacodynamic study was carried out in five healthy patients during surgery under general anaesthesia.

After single bolus doses of fazadinium 0.46–0.8 mg kg^{-1}, serial blood samples were taken and the plasma separated for assay. Simultaneously, the mechanical response of adductor pollicis to single supramaximal stimuli was recorded every 5 s on magnetic tape.

Plasma concentrations were estimated by Pastorino's fluorimetric method, and fitted in each case to a bi-exponential decay function by the method of maximum likelihood. Comparison of plasma concentrations with twitch suppression showed that while log-concentration varied linearly with twitch suppression during the late offset phase, earlier comparisons showed gross hysteresis.

Using a method previously described (Hull et al., 1978), the time-course of drug concentration in the biophase was calculated. When biophase log-concentrations were compared with simultaneous values for twitch suppression, a hysteresis-free sigmoid relationship was obtained in each case.

Wagner (1968) suggested that sigmoid concentration/response curves of this type could be characterized by the function $E = (E_{max}\,(C)^s)/(1/Q+(C)^s)$ where Q and s are constants. The constants can be readily deduced from a Hill plot ($\ln E/1-E$ v. $\ln C$), which should, in a system conforming to Michaelis–Menten kinetics, be linear. Data from all five subjects conformed to this hypothesis, with consistent values of s and $E.C._{50}$ (table I).

TABLE I. *Parameters of the Hill plots for five subjects.* s = *gradient;* $Q = E/(1-E)$ *when* $\ln C = 0$*;* $E.C._{50}$ = *biophase concentration when* $\ln E/(1-E) = 0$*, i.e. at* 50% *twitch suppression*

	Subject					
	A	B	C	D	E	Mean
s	4.25	4.68	5.32	3.91	4.16	4.46
Q	0.84	0.99	1.66	0.84	0.90	1.05
$E.C._{50}$ (μg ml^{-1})	1.04	1.00	0.91	1.05	1.02	1.00

A complete pharmacodynamic model based upon biophase kinetics and Wagner's sigmoid function was constructed for each subject. Families of dose–response curves (over the time-period of the original observations) showed that fazadinium is much less cumulative than pancuronium, and has a significantly faster onset in equipotent doses.

REFERENCES

Duvaldestin, P., Henzel, D., Demetrion, M., and Desmonts, J. M. (1978). *Br. J. Anaesth.*, **50**, 773.
Hull, C. J., Van Beem, H., McLeod, K., Sibbald, A., and Watson, M. J. (1978). *Br. J. Anaesth.*, **50**, 1113.
Wagner, J. G. (1968). *J. Theoret. Biol.*, **20**, 173.

CONTROL OF NEUROMUSCULAR BLOCKADE BY EXTERNAL FEEDBACK MECHANISMS

A. J. ASBURY, B. H. BROWN AND D. A. LINKENS
Departments of Anaesthesia, Medical Physics and Control Engineering, Sheffield University

It may be a problem to gauge the correct dose of a drug when the pharmacokinetics are unknown. In most instances the anaesthetist solves the problem when using neuromuscular blockers (NMB), by titrating the dose to the patient's response and adjusting dosage to maintain surgically acceptable paralysis. The authors have designed and constructed a feedback system which assesses the degree of neuromuscular blockade and automatically administers the appropriate dose of NMB to maintain paralysis at a predetermined level.

An electronic clock initiates stimulation of the patient's ulnar nerve using single supramaximal stimuli at 10-s intervals. The electromyogram evoked by the single stimulus is recorded by surface electrodes positioned over the small muscles of the hand. The signal is then filtered, integrated, rectified and stored as a d.c. voltage. This latter voltage is compared with a reference voltage which represents the desired degree of paralysis. The difference in the signals is then applied to a peristaltic pump which determines the rate of infusion of the NMB. Pancuronium was diluted in a standard infusion burette and passed via a sterile pump winding to the patient. In the event of power failure the pump remains occlusive, thus protecting the patient against over-dosage. Ten patients were studied during major upper abdominal surgery; the anaesthetic was selected to minimize pharmacological modification of the response to the neuromuscular blocker. Once apnoea had been induced by fentanyl 5.0 μg kg^{-1} and droperidol 0.1 mg kg^{-1} the patients' lungs were ventilated with nitrous oxide and oxygen and baseline e.m.g. values were obtained.

Muscle paralysis was produced using a bolus dose of pancuronium 20.0 μg kg^{-1}. Two minutes later the patient was connected to the pump and controlling apparatus which had been set to maintain paralysis at 80%. At the end of the period of control the residual paralysis was reversed using atropine and neostigmine. Venous blood samples were drawn at 5-min intervals during the period of controlled paralysis and subsequently assayed for pancuronium bromide using a fluorimetric method (Kersten, Meyer and Agoston, 1973).

The control of paralysis has been divided arbitrarily into two periods, the first is when the degree of neuromuscular blockade increased towards 80% of the baseline value. During this period 10 patients required a mean dose of 47.5 μg kg^{-1}. The mean time taken to reach 80.0% was 9.4 min. In all but one patient 80% paralysis was reached. The second period commenced when the patient's paralysis decreased to less than 80%. Under these circumstances the equipment began to adjust the dose of pancuronium to maintain a steady level of paralysis. As pancuronium was being removed constantly from the receptor sites at the neuromuscular junction, it was replaced by more pancuronium provided at a rate determined by the controller. During this second period the blood concentrations of pancuronium were constant and the consumption of pancuronium varied from 0.31 to 59 μg kg^{-1} min^{-1} achieving a range of paralysis from 72 to 78%. This study has demonstrated that the automatic control of paralysis is feasible using a relatively simple feedback mechanism. Such a system permits the achievement of good relaxation for upper abdominal surgery with the minimal dosage of neuromuscular blocking agent. The system so permits the easy evaluation of possible drug interactions (e.g. antibiotics), and abnormalities in neuromuscular transmission.

REFERENCE

Kersten, U. W., Meyer, D. K. F., and Agoston, S. (1973). *Clin. Chim. Acta*, **44**, 59.

RECOVERY FROM NEUROMUSCULAR BLOCKADE BY ATRACURIUM

R. Hughes, Tessa M. Hunt and J. P. Payne
Research Department of Anaesthetics, Royal College of Surgeons of England and St Peter's Hospitals, London

A preliminary evaluation in anaesthetized man has shown that atracurium is a potent competitive neuromuscular blocking agent with no cardiovascular side-effects at doses required for neuromuscular paralysis (Hunt, Hughes and Payne, 1980). Further studies have been carried out in anaesthetized patients in whom recovery from neuromuscular blockade by atracurium has been compared with that of other competitive blocking agents using techniques previously described (Hughes, Ingram and Payne, 1976).

In a total of 22 patients, i.v. doses of atracurium 0.2–0.6 mg kg^{-1} produced complete block of the tetanic responses of the adductor pollicis muscle. Tests of significance showed that the onset and the duration of full block were dose-dependent (table I). In contrast, once recovery had begun there was no significant difference either in the time taken to achieve 95% recovery of the peak tetanic contraction or in the rate constants for recovery of the sustained tetanus calculated from the slopes of the regression lines. Thus, it is interpreted that the recovery phase from neuromuscular blockade after atracurium was independent of dose.

Rate constants for recovery (per cent per min) of the sustained tetanus after blockade by atracurium were then compared with those for other agents using groups of five to seven patients for each drug: with atracurium 0.2 mg kg^{-1} a mean value of 12.5 ± 1.3 was obtained; with fazadinium 0.4–0.8 mg kg^{-1}. $5.5 \pm 1.3^{**}$; with tubocurarine 0.2 mg kg^{-1} $5.4 \pm 1.4^{**}$; with gallamine 1.0–1.6 mg kg^{-1} $4.0 \pm 0.8^{***}$; with pancuronium 0.05–0.06 mg kg^{-1} $3.9 \pm 1.9^{**}$; and with dimethyl tubocurarine 0.075–0.2 mg kg^{-1} $2.6 \pm 1.1^{***}$ (significant differences from atracurium: $^{**}P < 0.01$; $^{***}P < 0.001$). These results show that the rate of recovery of the sustained tetanus after neuromuscular blockade by atracurium was significantly faster than that of the other competitive neuromuscular blocking agents studied.

Table I. *Tetanic responses of the adductor pollicis muscle after neuromuscular blockade by atracurium* 0.2 *mg kg* $^{-1}$ *in comparison with those at* 0.3 *and* 0.6 *mg kg*$^{-1}$ *(mean ± SEM). Significant differences from* 0.2 *mg kg*$^{-1}$: $^{*}P < 0.05$, $^{***}P < 0.001$

Dose (mg kg^{-1})	Onset of max effect (min)	Duration of max effect (min)	95% recovery of peak contraction (min)	Rate constant for sustained tetanus (% min^{-1})
0.2 ($n = 9$)	2.8 ± 0.3	5.6 ± 0.6	28.9 ± 2.3	12.0 ± 1.0
0.3 ($n = 7$)	$1.9 \pm 0.1^{*}$	$15.5 \pm 1.8^{***}$	34.9 ± 1.9	10.1 ± 0.6
0.6 ($n = 6$)	$1.2 \pm 0.1^{***}$	$33.7 \pm 3.0^{***}$	34.5 ± 4.4	12.4 ± 1.4

REFERENCES

Hughes, R., Ingram, G. S., and Payne, J. P. (1976). *Br. J. Anaesth.*, **48**, 969.

Hunt, T. M., Hughes, R., and Payne, J. P. (1980). *Br. J. Anaesth.*, **52** (in press).

EFFECTS OF HALOTHANE AND HYPOCAPNIA ON COLON BLOOD FLOW IN THE DOG

A. R. Aitkenhead, D. G. Gilmour, A. P. Hothersall and I. McA. Ledingham
University Department of Surgery, Western Infirmary, Glasgow

Depending on the site of colonic anastomosis, the frequency of dehiscence may be as great as 69% (Goligher, Graham and DeDombal, 1970) and the mortality following clinically evident anastomotic dehiscence is about 35%. The blood supply to the colon is an important factor in maintaining an intact anastomosis (Everett, 1974). A dog model has been developed by the authors (Gilmour et al., 1980) to ascertain the effect of various factors which alter colon blood flow and may therefore have an effect on the healing of colon anastomoses. The present study was designed to investigate the effects of halothane on colon blood flow during normocapnia and hypocapnia.

Cardiac output, systemic arterial and right atrial pressures were recorded in 11 artificially ventilated dogs anaesthetized with pentobarbitone 40 mg kg^{-1}. Following splenectomy, a catheter was positioned with its tip in the cranial mesenteric artery just proximal to the branch supplying the colon. A second catheter was positioned in the main marginal vein of the colon. Colon blood flow was measured by injecting xenon-133 500 μCi through the mesenteric artery catheter and recording its clearance from the colon with a collimated scintillation counter. Blood samples were obtained from the catheter in the marginal vein for estimations of blood-gases, and blood lactate and

TABLE I. *Measurements obtained during normocapnia and hypocapnia before and during the administration of halothane in 11 dogs (mean ± SEM).* **$P < 0.05$ compared with normocapnia;* †*$P < 0.05$ compared with corresponding value before halothane administration*

	Before halothane		Halothane	
	Normocapnia	Hypocapnia	Normocapnia	Hypocapnia
Colon blood flow (ml 100 g^{-1} min^{-1})	41.90 ± 3.0	31.80 ± 2.3*	48.50 ± 1.6†	33.00 ± 1.0*
Colon vascular resistance (units)	3.64 ± 0.45	3.91 ± 0.52	2.09 ± 0.15†	2.61 ± 0.19*†
Total peripheral resistance (units)	28.16 ± 1.86	20.91 ± 1.47*	26.11 ± 1.99	19.71 ± 1.72*
Arterial lactate/pyruvate	8.20 ± 1.0	13.40 ± 1.7*	11.30 ± 1.4	14.50 ± 2.0*
Colon lactate/pyruvate	10.30 ± 1.4	13.70 ± 1.0*	8.10 ± 1.0	13.90 ± 2.6*
Colon oxygen consumption (ml 100 g^{-1} min^{-1})	1.04 ± 0.15	1.17 ± 0.21	0.80 ± 0.10†	0.79 ± 0.11†

pyruvate concentrations. Measurements were made during normocapnia (mean arterial P_{CO_2} 5.2 kPa) and repeated during hypocapnia (mean arterial P_{CO_2} 2.5 kPa). Halothane was added to the inspired gas mixture at a concentration which resulted in a mean arterial pressure of 100 mm Hg. Measurements were then repeated during normocapnia and hypocapnia.

Results are presented in table I. Hypocapnia caused significant decreases in colon blood flow and total peripheral resistance, and increases in arterial and colon lactate/pyruvate ratios, both before and during halothane administration. Colon vascular resistance increased significantly in response to hypocapnia during halothane administration. Halothane produced a significant decrease in colon vascular resistance and colon oxygen consumption, irrespective of arterial P_{CO_2}. There was a significant increase in colon blood flow during halothane administration at normocapnia, but colon blood flow during hypocapnia was similar before and during halothane administration.

If these changes occur in man, the administration of halothane will result in an increase in colon blood flow which may be of benefit in patients undergoing a colon anastomosis. However, these effects will be negated by hyperventilation.

REFERENCES

Everett, W. G. (1974). *Ann. R. Coll. Surg. Engl.*, **55**, 31.

Gilmour, D. G., Douglas, I. H. S., Aitkenhead, A. R., Hothersall, A. P., Horton, T. W., and Ledingham, I. McA. (1980). *Cardiovasc. Res.*, **14**, 11.

Goligher, J. C., Graham, N. G., and DeDombal, F. T. (1970). *Br. J. Surg.*, **57**, 109.

SOME EFFECTS OF I.V. ANAESTHETIC AGENTS ON THE CANINE SMALL INTESTINE

T. E. J. HEALY, D. F. EVANS, G. E. FOSTER AND A. SYED
Department of Surgery (Anaesthetics) Nottingham, Medical School

Fast spike electrical activity recorded from the small intestine has been shown to correlate well with mechanical activity in the chronic canine preparation (Bass and Wiley, 1965). We have confirmed this finding in an examination of the effect of exogenous porcine glucagon (Novo Lab.) on the mechanical and electrical activity recorded from the canine small intestine (Foster et al., 1979).

Sleep doses of i.v. anaesthetic agents were administered to nine greyhound dogs in which bipolar silver/silver chloride electrodes had previously been implanted to measure the electrical activity of the small intestine. Some animals (three) also had strain gauges implanted with the electrodes to confirm the relation between fast spike electrical activity and mechanical activity. Electrical and mechanical activity was recorded onto magnetic tape and quantified by digital computer analysis.

Thiopentone 500 mg, ketamine 200 mg or minaxolone 50 mg was administered i.v. to fasted animals during phase 1 of the interdigestive cycle (Carlson, Bedi and Code, 1972) confirmed by recording the electrical and mechanical activity before injection of the anaesthetic agent.

Thiopentone 500 mg (18 separate recordings, six dogs) was followed by a marked increase in mechanical and fast spike electrical activity ($P < 0.001$) which occurred within 2 min of the injection and lasted for several minutes (7.7 ± 0.6 SEM). This effect did not occur when thiopentone was preceeded by either atropine 1.2 mg or pentolinium 5 mg (six separate recordings, three dogs). Ketamine 200 mg (six separate recordings, three dogs) had no effect on the resting interdigestive mechanical or electrical activity; however when thiopentone 500 mg (six separate recordings, three dogs) was administered after ketamine, marked mechanical fast spike electrical again occurred.

If these findings are confirmed in human studies, they will lend support to the use of atropine premedication, before induction of anaesthesia with thiopentone, for patients who have a recently constructed intestinal anastomosis.

REFERENCES

Bass, P., and Wiley, J. N. (1965). *Am. J. Dig. Dis.*, **10**, 183.

Carlson, E. M., Bedi, B. S., and Code, C. F. (1972). *Am. J. Physiol.*, **222**, 1027.

Foster, G. E., Hardcastle, J. D., Evans, D. F., Wright, J. W., and Slater, E. (1978). *Br. J. Pharmacol.*, **64**, 475P.

A MODEL-BASED COMPARISON OF TWO HEAD INJURY TREATMENTS

A. M. S. BLACK AND R. I. HARRIS
Nuffield Department of Anaesthetics, University of Oxford, Radcliffe Infirmary, Oxford

Between 1970 and 1975, patients with diffuse brain swelling following head injury were treated in Auckland Hospital Department of Critical Care by sedation and elective ventilation of the lungs. This differs from conventional treatment. An international bank of data on patients treated conventionally for head injuries (Jennett et al., 1976) has been used as a standard in comparisons against less conventional treatment (Becker et al., 1977).

Comparisons have been difficult because of dissimilarities between series in respect of some determinants of outcome. Also, the similarities which have been demonstrated in establishing the comparability of series have been with the best neurological signs in the International Data Bank cases for the 24 h after the onset of coma. This model-based comparison addressed itself to these difficulties.

Information on the state of Auckland patients before treatment, retrieved from case notes, and on their outcome was codified and fitted to a form of linear logistic model (McCullach, 1980) for describing from potential determinants of outcome the probabilities with which an outcome would fall into each of a set of outcome classes. The model parameters for fits to a number of subsets of the Auckland data were computed using the method of maximum likelihood. The fits to the data were good as judged from the distributions of actual and described outcome within prognostic categories defined from the fits. Different fits identified fairly consistently the significant determinants of outcome as pupil size, coma score, age, haematoma and extracranial factors.

Data on 105 Auckland patients, combined with correspondingly coded data on 100 Data Bank patients, were submitted to a common fit to the model using, as potential determinants of outcome, the above factors and a dummy variable indicating source of patients—Auckland or Data Bank. The Data Bank cases were entered with either their worst or their best pupil and coma scores for the first 24 h after coma. In the former case, the dummy variable was not significant. In the latter case it was and indicated a significantly better outcome in Auckland.

Sedation of Auckland cases made it impossible to judge whether their pupil and coma scores corresponded more with the 24-h best or worst from the Data Bank. No conclusions can be drawn about the relative merits of Auckland and Data Bank treatment. Implications from previous comparisons should be reconsidered in this light.

REFERENCES

Becker, D. P., Miller, J. D., Ward, J. D., Greenberg, R. P., Young, H. F., and Sakalas, M. D. (1977). *J. Neurosurg.*, **47**, 491.

Jennett, B., Teasdale, G., Braakman, R., Minderhoud, J., and Knill-Jones, R. (1976). *Lancet*, **1**, 1031.

McCullach, P. (1980). *J. R. Statistical Soc.* Ser. B, **42** (in press).

Br. J. Anaesth. (1980), **52**, 637

CORRESPONDENCE

EXTRADURAL PETHIDINE

Sir,—We have reported the remarkable efficacy of 2 mg of morphine injected to the extradural space in the treatment of chronic pain (Bapat, Kshirsagar and Bapat, 1979). We have now tried extradural pethidine on the grounds that it is more easily available in India than is morphine and it has some notable differences in action, for example local anaesthetic activity (Jaff and Martin, 1975).

Pethidine 10–15 mg in 10 ml of normal saline was injected at L3–L4 in four patients with peripheral vascular disease and one patient with chronic backache. There was complete relief of pain, onset 5–6 min and lasting for from 48 h to more than 7 days. There was no loss of other sensation.

Despite better penetration to c.s.f. the onset of analgesia was delayed as compared with our experience of morphine (1–2 min). This suggests a possible extradural site of action of morphine. In this connection it is interesting to note that meth-enkephalin has been identified on peripheral nerves (Hughes, Kosterlitz and Smith, 1977).

Aruna R. Bapat
Nilima A. Kshirsagar
R. D. Bapat
Bombay, India

REFERENCES

Bapat, A. R., Kshirsagar, N. A., and Bapat, R. D. (1979). Aspects of epidural morphine. *Lancet*, **2**, 583.

Hughes, J., Kosterlitz, H. W., and Smith, T. W. (1977). The distribution of methionine–enkephalin and leucine–enkephalin in the brain and peripheral tissues. *Br. J. Pharmacol.*, **6**, 639.

Jaff, J. H., and Martin, W. R. (1975). In *Pharmacological Basis of Therapeutics*, 5th edn (eds L. S. Goodman and A. Gilman), p. 264. London: Macmillan.

SMOOTH MUSCLE CONTRACTURE IN MALIGNANT HYPERPYREXIA

Sir,—Malignant hyperpyrexia (MH) appears to result from an abnormality in cellular Ca^{2+} metabolism and, *in vitro*, MH skeletal muscle shows increased contracture to halothane, caffeine, suxamethonium and K^+ both in man (Moulds and Denborough, 1974) and in pigs (Okumura, Crocker and Denborough, 1979). With this in mind we have examined drug-induced contractures in smooth muscle from MH-susceptible (MHS) swine.

Tracheae were obtained from four MHS swine and from four controls. From each pig four sections of trachea, 5 mm wide, were removed and the trachealis muscle and attached mucosa were dissected free. The preparations were superfused with Krebs solution 1.5 ml min^{-1} at 37 °C and changes in isometric tension were recorded as described previously (Mitchell and Denborough, 1979). The initial load was 2 g. At the end of the experiment the preparations were removed, gently blotted dry and weighed and the protein content was estimated (Lowry et al., 1951). There were no significant differences in the weights or protein contents of the muscle from control or MHS swine.

Halothane 3% did not produce contracture in the smooth muscle preparation from either the MHS or the control swine. Histamine produced only weak contractures in the pig trachea and there was no significant difference between the two groups (table I).

K^+ contracts tracheal smooth muscle by a depolarization-dependent influx of extracellular or membrane-bound Ca^{2+} whereas acetylcholine, at the concentration used, causes contracture by mobilizing more tightly bound intracellular Ca^{2+} (Kirkpatrick, 1975; Farley and Miles, 1977; Coburn, 1979). However, duplicate tracheal contractures induced by K^+ and acetylcholine showed no significant difference in MHS swine when compared with controls (table I).

TABLE I. *The effect of K^+, acetylcholine and histamine on tracheal preparations from malignant hyperpyrexia susceptible (MHS) swine and from controls. Values are mean ± SEM contracture in grams. Number of preparations in parentheses. P values calculated by Student's t test*

	MHS swine	Controls	*P*
K^+ 80 mmol $litre^{-1}$	7.05 ± 0.84 (15)	8.20 ± 1.02 (16)	> 0.4
Acetylcholine 10 μmol $litre^{-1}$	7.03 ± 0.88 (13)	6.46 ± 0.70 (16)	> 0.6
Histamine 100 μmol $litre^{-1}$	1.85 ± 0.42 (13)	2.79 ± 0.65 (16)	> 0.2

These investigations suggest that smooth muscle is not affected by the membrane abnormality which occurs in malignant hyperpyrexia.

H. W. Mitchell
M. A. Denborough
Canberra

REFERENCES

Coburn, R. F. (1979). Electromechanical coupling in canine trachealis muscle: acetylcholine contractions. *Am. J. Physiol.*, **236**, 177.

Farley, J. M., and Miles, P. R. (1977). Role of depolarization in acetylcholine-induced contractions in dog trachealis muscle. *J. Pharmacol. Exp. Ther.*, **201**, 199.

Kirkpatrick, C. T. (1975). Excitation and contraction in bovine tracheal smooth muscle. *J. Physiol. (Lond.)*, **244**, 263.

Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J. (1951). Protein measurement with the Folin phenol reagent. *J. Biol. Chem.*, **193**, 265.

Mitchell, H. W., and Denborough, M. A. (1979). Anaphylaxis in guinea-pig peripheral airways *in vitro*. *Eur. J. Pharmacol.*, **54**, 69.

Moulds, R. F. W., and Denborough, M. A. (1974). Biochemical basis of malignant hyperpyrexia. *Br. Med. J.*, **2**, 241.

Okumura, F., Crocker, B. D., and Denborough, M. A. (1979). Identification of susceptibility to malignant hyperpyrexia in swine. *Br. J. Anaesth.*, **51**, 171.

MECHANISM OF ACTION OF KETAMINE

Sir,—A survey of the recent literature indicates that the well-known cardiovascular stimulation seen during ketamine-induced anaesthesia is a result, in part, of potentiation of catecholamines (Uptake$_1$)—a cocaine-like activity (Nedergaard, 1973). We have shown that ketamine potentiated vascular smooth muscle, not by a cocaine-like effect, but by inhibition of extraneuronal catecholamine uptake (Uptake$_2$) (Lundy, Colhoun and Gowdey, 1972; Lundy, Gowdey and Colhoun, 1976). Recent unpublished observations from our laboratory were that ketamine possessed little if any cocaine-like activity in vascular tissue.

Salt, Barnes and Beswick (1979) showed that a large portion of uptake inhibition in heart tissue was also a result of inhibition of extraneuronal mechanisms. A critical review of the literature would dispel the apparent acceptance of ketamine as an inhibitor of Uptake$_1$ in vascular smooth muscle at least. Moreover, ketamine, although apparently possessing some cocaine-like activity in some tissues, cannot be referred to as a cocaine-like compound without reference to the tissues examined and to the importance of Uptake$_2$.

PAUL M. LUNDY
Ralston, Alberta, Canada

REFERENCES

Lundy, P. M., Colhoun, E. H., and Gowdey, C. W. (1972). Some effects of ketamine on smooth muscle. Fifth Int. Congr. Pharmacol. San Francisco, p. 144.

—— Gowdey, C. W., and Colhoun, E. H. (1976). The actions of ketamine on vascular smooth muscle. *Arch. Int. Pharmacodyn. Ther.*, **220**, 213.

Nedergaard, O. A. (1973). Cocaine-like effect of ketamine on vascular adrenergic neurons. *Eur. J. Pharmacol.*, **23**, 153.

Salt, P. J., Barnes, P. K., and Beswick, F. J. (1979). Inhibition of neuronal and extranueronal uptake of noradrenaline by ketamine in the isolated perfused rat heart. *Br. J. Anaesth.*, **51**, 835.

ANAESTHESIA FOR LARYNGOSCOPY

Sir,—In the past few years several techniques of anaesthesia for direct laryngoscopy utilizing the principle of jet ventilation with oxygen or Entonox through the open airway have been described (Smith, Babinski and Petruscak, 1974; Poling, Wolfson and Siker, 1975; Gillick, 1976; Tobias, Nassar and Richards, 1977; Pybus, O'Connor and Henville, 1978). A recent fatal incident during anaesthesia with the technique using the Nuffield Anaesthetic Ventilator (Pybus, O'Connor and Henville, 1978) in a child of 4 years undergoing laryngoscopy for removal of laryngeal papillomata highlights a hazard of these techniques. Anaesthesia was induced with i.v. thiopentone followed by suxamethonium. Following inspection of the larynx, topical anaesthesia was induced with 10% lignocaine 5 mg kg^{-1}. An 8-f.g. catheter was introduced through the vocal cords until the tip was estimated to lie in the midtracheal region. The catheter was connected to a Penlon Nuffield Anaesthetic Ventilator driven by Entonox supplied from a cylinder fitted with an Airmed reducing valve giving an output pressure of 410 kPa. The flow rate was set to provide 0.25 litre s^{-1} and inspiratory and expiratory times set to 1 s. Gross surgical emphysema appeared in the neck and face as the abdomen became distended and rigid. The catheter was removed and following tracheal intubation 100% oxygen was given by IPPV. The peripheral pulses were absent and full resuscitative measures were instituted. A massive right pneumothorax was drained, after which the heart sounds reappeared and peripheral pulses became palpable. Despite the rapid institution of a regime for the treatment of cerebral hypoxia, brain death occurred. At postmortem there was no gross evidence of damage to the tracheobronchial tree or lungs.

The cause of this tragedy must have been the presence of excessive pressure within the lungs. Whenever this technique is used it is essential to ensure (a) the correct size (length and width) of catheter in relation to age, (b) a guaranteed expiratory pathway, (c) minimal inspiratory time, (d) adequate expiratory time and (e) the monitoring of chest movement during each inspiration and expiration.

ELENA VIVORI
Liverpool

REFERENCES

Gillick, J. S. (1976). The inflation-catheter technique of ventilation during laryngoscopy. *Can. Anaesth. Soc. J.*, **23**, 534.

Poling, H. E., Wolfson, B., and Siker, E. S. (1975). A technique of ventilation during laryngoscopy and bronchoscopy. *Br. J. Anaesth.*, **47**, 382.

Pybus, D. A., O'Connor, A. F., and Henville, J. D. (1978). Anaesthesia for laryngoscopy: a technique using the Nuffield Anaesthetic Ventilator. *Br. J. Anaesth.*, **50**, 501.

Smith, R. B., Babinski, M., and Petruscak, J. (1974). A method of ventilating patients during laryngoscopy. *Laryngoscope*, **84**, 553.

Tobias, M. A., Nassar, W. Y., and Richards, D. C. (1977). Naso-tracheal jet ventilation for microlaryngeal procedures. *Anaesthesia*, **32**, 359.

ROYAL SOCIETY/JAPANESE SOCIETY FOR THE PROMOTION OF SCIENCE—FELLOWSHIPS

Sir,—May I use your columns to draw attention to an agreement reached recently between the Royal Society and the Japanese Society for the Promotion of Science, for a number of new fellowships to be established. Under the terms of the agreement it would be possible for a member of a British department of anaesthesia which already has links with Japan to apply to undertake research in a Japanese department for a period of between 12 and 24 months.

During his recent visit to this country, Professor Kenjiro Mori indicated that he would welcome a British anaesthetist to study neurophysiology in relation to anaesthesia in his department in Kyoto. Professional communications could be conducted in English and the University of Kyoto maintains a guest house for the accommodation of overseas visiting workers. Enquiries and applications should be addressed to the Executive Secretary of the Royal Society at 6 Carlton House Terrace, London SW1Y 5AG, but I should also be pleased to offer further information to anyone who is interested in taking advantage of this very unusual opportunity.

J. F. NUNN
Division of Anaesthesia,
Clinical Research Centre,
Watford Road,
Harrow, Middx HA1 3UJ

BOOK REVIEWS

Dental Anaesthesia and Analgesia (Local and General). Edited by Gerald D. Allen. Published by Williams and Wilkins, Baltimore, London. Pp. 446; illustrated; indexed. Price $29.95.

The label "second edition" should not be taken to imply that this is a superficially revised version of the original book which was published in 1972. It is, in fact, a rearranged and much more comprehensive, coherent and authoritative work, which reflects the progress which has been made in the concept and philosophy of pain control in dentistry in the intervening years.

Pain control in dentistry is, indeed, still a controversial subject and, even today, there are those who doubt whether systemic pharmacological analgesia and sedative medication is ever necessary in areas of dental practice such as conservation. It is not surprising, therefore, that Dr Allen and his colleagues choose to start by considering the value of non-invasive techniques such as acupuncture and hypnosis and then, after a very comprehensive chapter on patient evaluation and preparation, go on to cover local analgesia in detail—a topic which was not considered at all in the first edition. The book then continues its logical progression through inhalation and i.v. sedation, to full general anaesthesia for oral surgery; finally the concluding chapters deal with the factors which govern the selection of the appropriate "pain control modality", emergencies occurring during the conduct of sedation, analgesia and general anaesthesia and last, but by no means least, with the management of chronic oro-facial pain. The book lays emphasis on the selection of a proper method of pain control for the individual patient undergoing a specific operation to which he is expected to react in a particular way. Erudite practical sections are interspersed with sound theoretical discussions. Emphasis is laid on the fact that outpatient anaesthesia is for relatively fit patients only, and the sage advice that "if general anaesthesia is considered essential for the patient general anaesthesia should be used deliberately", should be heeded by all who practise so-called "twilight sleep" or "ultra-light" techniques—methohexitone is firmly catalogued amongst the i.v. general anaesthetic agents in this volume.

This edition, like its predecessor, must be studied against the background of current practice in the United States. In that country the spectrum of oral surgery procedures undertaken in the outpatient office is far wider than those ever attempted in outpatient dental surgeries in Dr Allen's native United Kingdom, and dental and oral surgeons have considerably greater exposure to anaesthesia, both in training and in practice, than is customary in Great Britain today. This particular text is, in fact, a comprehensive textbook for American anaesthetists and oral surgeons who practice anaesthesia. This particular orientation should not, however, discourage close study of this work by established British anaesthetists and their trainees. The concepts both of theory and of practice are sound and can be applied well beyond the limited fields of oral and dental surgery—although some reservations must be expressed about Dr Allen's continued advocacy of the "semisupine" posture for general anaesthesia for dentistry.

The book is well produced, apart from the misplaced block for Fig. 16. 11, which at first sight seems to illustrate a very bizarre head position for intubation. The volume is strongly and adequately bound, but those familiar with the first edition will miss the attractive odontological artwork on its cover.

T. B. Boulton

Local Analgesia. By C. Jolly. Published by H. K. Lewis & Co., London. Pp. 143; illustrated; indexed. Price £5.

The first edition of Dr Jolly's book on local anaesthesia first appeared in 1962 and the current edition does not differ greatly from it. Dr Jolly is clearly an enthusiast for regional anaesthesia and is at his best writing about the techniques of which he has most experience. When he ventures into the more scientific aspects of the subject he seems less at ease, and little of the considerable advances that have been made in the past two decades are to be found in his book.

The text is quickly and easily read. Much is written in a chatty style which may be helpful in looking up an unusual nerve block such as lumbar sympathectomy, but is irritating when describing patient management in general under the heading of "Block Technique". The author seems unsure to whom he is directing his efforts—nurse, house officer on his first day in the theatre, or medical student?

The line drawings are simple, but not to be compared with other books on the subject such as Eriksson's *Illustrated Handbook of Local Anaesthesia.*

While not for the experienced practitioner in the field of local anaesthesia, this book may be well liked by the anaesthetist or surgeon wishing to understand the mechanics of a particular block.

D. B. Scott

Lactate in Acute Conditions. International Symposium on Lactate in Acute Conditions, Basel, 1978. Edited by H. Bossart and C. Perret. Published by S. Karger, Basel. Pp. 148; illustrated; indexed. Price $53.50.

Roche have recently introduced an electrochemical device for the rapid estimation of lactate and a Symposium was organized in 1978 by this Company to review some of the recent developments in lactate metabolism. This book reports the proceedings of the meeting and is divided into four sections covering basic aspects, perinatal medicine, medicine and surgery, and lactate in cerebrospinal fluid.

The section on perinatal medicine is particularly interesting. Three studies investigate the possibility that the rapid estimation of blood lactate in the fetus and newborn may be a valuable aid to the diagnosis and treatment of the asphyxiated infant. Unfortunately the results are mostly inconclusive. Not surprisingly, the remainder of the book contains little information that has not been published elsewhere. It was a pleasure to find the usual polished presentations from the British representatives, the "Metabolic Trinity", Professors Cohen, Alberti and Woods.

I cannot recommend this book to those who are seeking a thorough explanation of lactate metabolism; their needs are best served by the excellent publication *Clinical and Biochemical Aspects of Lactic Acidosis* by Cohen and Woods. However, research workers with a particular interest in lactate metabolism will find much of interest and I advise them to obtain a copy.

G. M. Hall

REFERENCE

Cohen, R. D., and Woods, H. F. (1976). *Clinical and Biochemical Aspects of Lactic Acidosis.* Oxford and Edinburgh: Blackwell Scientific Publications.

Cardiovascular Physiology for Anesthesiologists. By R. J. Gordon, M. B. Ravin and G. R. Daicoff. Published (1979) by Charles C. Thomas, Springfield, Illinois. Pp. 209; illustrated. Price $19.75.

This short American book is not a comprehensive review of current thoughts on the physiology of the cardiovascular system. It is the stated intention of the authors that it should be "an introduction to current advances in the field of cardiovascular physiology". It cannot therefore be recommended as a reference textbook for the general reader or for examination candidates. The aim of the book is to provide a text for those with a specific interest in the perioperative period. The approach is theoretical in nature and would provide practical help only for those with facilities for carrying out sophisticated cardiovascular monitoring and measurements.

There are seven chapters on various aspects of cardiovascular physiology, including cardiac output, cardiac function curves, the coronary circulation, and (the most informative of these for your reviewer) blood rheology. Two other chapters deal with electrocardiography for the operating room and anaesthesia for surgical correction of congenital heart disease. Inevitably, American attitudes are strongly reflected particularly in these last two chapters.

Each chapter is followed by a lengthy reference list and by a series of questions on the topic of the foregoing chapter. The questions seemed out of place considering the readership at which the book appears to be aimed.

The book is well produced and the illustrations and diagrams are clear.

J. P. Vance

Muscle Relaxants, 2nd edn. By S. A. Feldman. Published by W. B. Saunders. Pp. 240; illustrated; indexed. Price £11.50.

The publication of a second edition must reflect the success of the first edition and the need to update a 6-year-old book covering a rapidly expanding and developing field. This book is in the series *Major Problems in Anesthesia* under the overall editorship of Professor W. K. Hamilton who succeeds Professor W. W. Mushin, the editor of the first three volumes. The second edition of *Muscle Relaxants* is 50 pages longer than the first edition and is printed in a slightly larger format.

The author has adopted the same logical sequence of chapters, with the earlier chapters dealing with the more theoretical concepts and the later chapters devoted to clinical aspects of the use and abuse of relaxant drugs. Much of the book has been rewritten, expanded and improved. The illustrations are clear and benefit from the larger size of page, and there are many more references, the early papers being particularly well represented.

There are several chapters dealing with the mode of action of the relaxants, and by reshuffling and adding more recent work this part has been made more meaningful than in the previous edition. Dr Feldman has added two useful chapters on drug interactions and the measurement of neuromuscular blockade.

The author has retained a pleasing conciseness which greatly helps the reader to obtain important information with a minimum of effort. I can recommend this book to all anaesthetists as a very readable account of a topic which is becoming increasingly complex. Being a monograph, it has the great advantage over edited works of uniformity of style and continuity of thought, and the only criticism can be that it emphasizes one school of thinking.

F. R. Ellis

Monitoring Cerebral Function: Long-term Recording of Cerebral Electrical Activity. By Pamela Prior. Published by Elsevier/North-Holland Biomedical Press, Amsterdam, New York and Oxford. Pp. 366+xi; illustrated; indexed. Price $56.50.

There are at least two aspects of brain function that anaesthetists would wish to monitor given appropriate cheap reliable apparatus. First there are a number of occasions when it is useful to know that the brain is being perfused with oxygenated blood such as during hypotensive anaesthetic techniques, cardiopulmonary bypass and carotid artery surgery. In these the electrical activity can be used as the basis of the monitoring. Second, anaesthetists use drugs which modify the activity of the brain and it is not easy to assess the extent of that change especially in paralysed patients. Whilst much can be gained from studies of the electroencephalogram and from more sophisticated developments such as the recording of evoked potentials the apparatus is cumbersome, expensive and demands virtually full time attention.

In 1969 Maynard, Prior and Smith described the Cerebral Function Monitor which uses two leads only to monitor cortical activity over the parietal lobes. The signal is amplified, filtered, compressed and rectified and appears as a trace on a slow-moving chart recorder. The lower edge defines the mean lowest activity and the width of the band shows the variation in activity.

This book by Dr Prior reviews the uses the Cerebral Function Monitor has had over the first decade, emphasizing its values and discussing its limitations. In considering cerebral perfusion and oxygenation it is very useful, but apart from relatively simple drug problems such as barbiturate coma or the control of epilepsy, its use to assess depth of anaesthesia is not so valuable. Providing it is run continuously from before the induction of anaesthesia it will help, but the subsequent height and variability of the trace cannot be assessed in isolation.

The book covers the needs for monitoring, the technical aspects of the machine and its use in clinical practice. The possibilities for future development are also discussed. The book is well written, clearly illustrated and should be essential reading for those who wish to know how they can monitor brain function in anaesthetic practice.

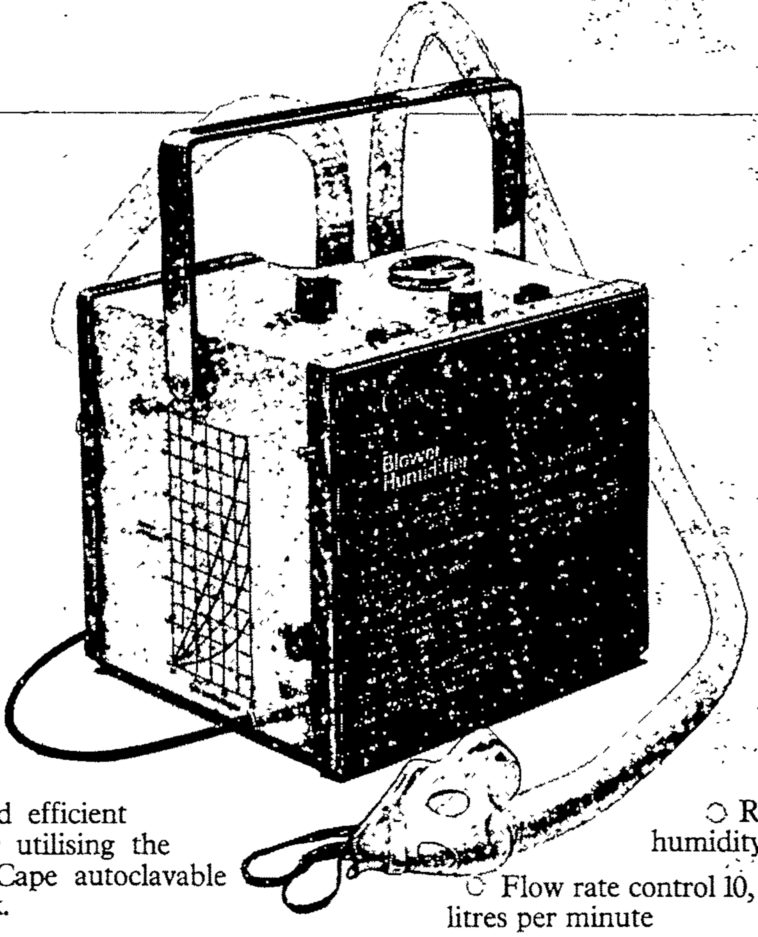
John Norman

Printed in Great Britain by John Wright and Sons Ltd, at The Stonebridge Press, Bristol BS4 5NU

© Macmillan Journals Ltd 1980

NEW

Blower Humidifier



A safe and efficient humidifier utilising the standard Cape autoclavable water tank.

- ○ Safety over temperature cut-out (70°C)
- ○ Water bath temperature adjustable 40°C-60°C
- ○ Relative humidity of 90-100%
- ○ Flow rate control 10, 20, 30 or 40 litres per minute
- ○ Bacterial filter
- ○ Fully autoclavable water tank
- ○ Disposable patient tubing and mask

Other products in the Cape range include ■ Cape 2000 Intensive Care Ventilator ■ T.C 50 Ventilator ■ Cape Waine MK. 3 Anaesthetic Ventilator ■ TTL Ventilation Failure Alarm ■ Anaesthetic accessories ■ Foot operated and wall mounted suction apparatus.

For full details on any of these products contact John Copson

Cape

Cape Engineering Company Limited,
The Cape, Warwick,
England, CV34 5DL
Telephone: 0926 496421
Telex: 31475

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 52, No. 6 *Published monthly* JUNE 1980

Annual subscriptions (post free): U.K. £22.50; U.S.A. and Canada U.S.$54, Airmail U.S.$120;
Rest of World £27.50, Airmail £50 ISSN 0007-0912

Subscription Department, Macmillan Journals Ltd, Brunel Road, Basingstoke, Hampshire RG21 2XS, England

CONTENTS

PAGE

EDITORIAL: Fentanyl and the metabolic response to surgery 561
G. M. Hall

EXPERIMENTAL

Changes of the cell bodies in the facial nucleus after facial nerve block 563
T. Totoki, K. Harano, Y. Aika and T. Kanaseki

Protective effect of steroids on cultured cells damaged by high concentrations of oxygen .. 567
J. E. Sturrock and G. H. Hulands

Halothane anaesthesia can block insulin stimulation of pyruvate dehydrogenase activity in mammary glands of 24-hour starved lactating rats.. 573
C. E. Hutchinson and H. G. Coore

Halothane improves the balance of oxygen supply to demand in acute experimental myocardial ischaemia 577
G. Smith, K. Rogers and J. Thorburn

Effect of low concentrations of halothane on the oxygen electrode 585
T. Maekawa, Y. Okuda and D. G. McDowall

CLINICAL INVESTIGATION

Effect of baricity on spinal anaesthesia with amethocaine 589
D. T. Brown, J. A. W. Wildsmith, B. G. Covino and D. B. Scott

Plasma atropine concentrations determined by radioimmunoassay after single-dose i.v. and i.m. administration 597
L. Berghem, U. Bergman, B. Schildt and B. Sörbo

Prolongation of thiopentone anaesthesia by probenecid 603
S. Kaukinen, M. Eerola and P. Ylitalo

Local reactions to i.v. diazepam in three different formulations 609
A. Schou Olesen and M. S. Hüttel

PAGE

Comparison of i.m. lysine acetylsalicylate and oxycodone in the treatment of pain after operation 613
K. Korttila, O. M. Pentti and J. Auvinen

CASE REPORTS

Perioperative considerations in the management of tracheotomy for the obstructive sleep apnoea patient. *Three illustrative case reports* 619
T. D. Rafferty, A. Ruskis, C. Sasaki and J. B. Gee

Progressive systemic sclerosis. Prolonged sensory blockade following regional anaesthesia in association with a reduced response to systemic analgesics 623
R. S. Neill

APPARATUS

A simple and inexpensive device for administration of continuous positive airway pressure breathing 627
M. Bagger

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Nottingham Meeting, March 21, 1980 .. 629

CORRESPONDENCE

Extradural pethidine 637
Smooth muscle contracture in malignant hyperpyrexia 637
Mechanism of action of ketamine 638
Anaesthesia for laryngoscopy 638
Royal society/Japanese society for the promotion of science—fellowships 638

BOOK REVIEWS

Dental Anaesthesia and Analgesia (Local and General) 639
Local Analgesia 639
Lactate in Acute Conditions 639
Cardiovascular Physiology for Anesthesiologists .. 640
Muscle Relaxants 640
Monitoring Cerebral Function: Long-term Recording of Cerebral Electrical Activity 640

EDITORIAL BOARD page ii

© MACMILLAN JOURNALS LTD, 4 LITTLE ESSEX STREET, LONDON WC2R 3LF